BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

Managing Editor, E. Cowles Andrus

Edward P. Carter
Charles R. Austrian
Arnold R. Rich
Paul G. Shipley
Frank R. Smith
George B. Wislocki

VOLUME XLVIII

THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND
1931

Medical Lib.
JAN 8 1931

BULLETIN
OF THE
JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XLVIII, No. 1 JANUARY, 1931

Contents

Congenital Syphilis of the Adrenal Gland. GEORGE LIDDLE FITE.... 1

The Cells Found in Tuberculous Tissues as Demonstrated by Vital and Supravital Staining. EDNA H. TOMPKINS AND R. S. CUNNINGHAM..... 8

Di-hydranol. Control of Intestinal Putrefaction in Man by Oral Administration of 2-4-Dihydroxyphenyl n-Heptane. VEADER LEONARD, M.D. AND WILLIAM A. FEIRER, M.D..... 25

Carcinoma of the Stomach in a Seventeen-Year-Old Girl. ALEXANDER MARBLE, M.D..... 39

Book Reviews..... 48

PUBLISHED MONTHLY
THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND
Made in United States of America

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, E. Cowles Andrus

EDITORIAL BOARD

Edward P. Carter
Charles R. Austrian
Arnold R. Rich
Paul G. Shipley
Frank R. Smith
George B. Wislocki

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, with covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly.

Subscriptions should be renewed promptly—To avoid a break in your series, subscriptions should be renewed promptly. The publishers cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Agents for the British Empire, except Canada: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, W.C. 2, London.

THE JOHNS HOPKINS PRESS

BALTIMORE, MARYLAND, U. S. A.

Medical
Faxon

CONGENITAL SYPHILIS OF THE ADRENAL GLAND[1]

GEORGE LIDDLE FITE

From the Department of Pathology, The Johns Hopkins University, Baltimore, Maryland

We have had occasion to examine microscopically the adrenal glands from some two hundred and fifty cases of congenital syphilis. In only about forty of these was there any abnormality whatever of the cellular structure of the gland to be observed, but some of these latter showed most striking changes attributable to syphilis. The rarity of involvement of the adrenal gland in the syphilitic process has been noted by many writers on this subject, and Hecker (11), in his statistical study of the frequency of the involvement of the various organs in congenital syphilis, found the adrenal gland affected less frequently than any other. Shortly after the demonstration of spirochaetes in the organs of congenitally syphilitic infants by von Gierke (5), Simmonds called attention to the regularity with which they may be found in the adrenal gland. In virtually every case of congenital syphilis at our disposal in which spirochaetes have been found they have been demonstrable in the adrenal gland. Their presence, often in great numbers, seems to give, however, no indication of the probability of any pathological alteration of the tissue. Indeed, the common lesion of the adrenal gland in congenital syphilis has been described as the presence of spirochaetes without other alteration.

About half of our cases have been in stillborn infants. Most of the other subjects had died in the first month or two of life, and the oldest had died at seven months of age. We were interested in the question of whether the pathological changes might be any different in those infants which had lived a few weeks or months from those which were stillborn, but we have not been impressed by any fundamental difference. The fact, as shown by Lewis and Pappenheimer (18), that the adrenal gland in the human being undergoes an involutionary process

[1] Submitted for publication August 14, 1930.

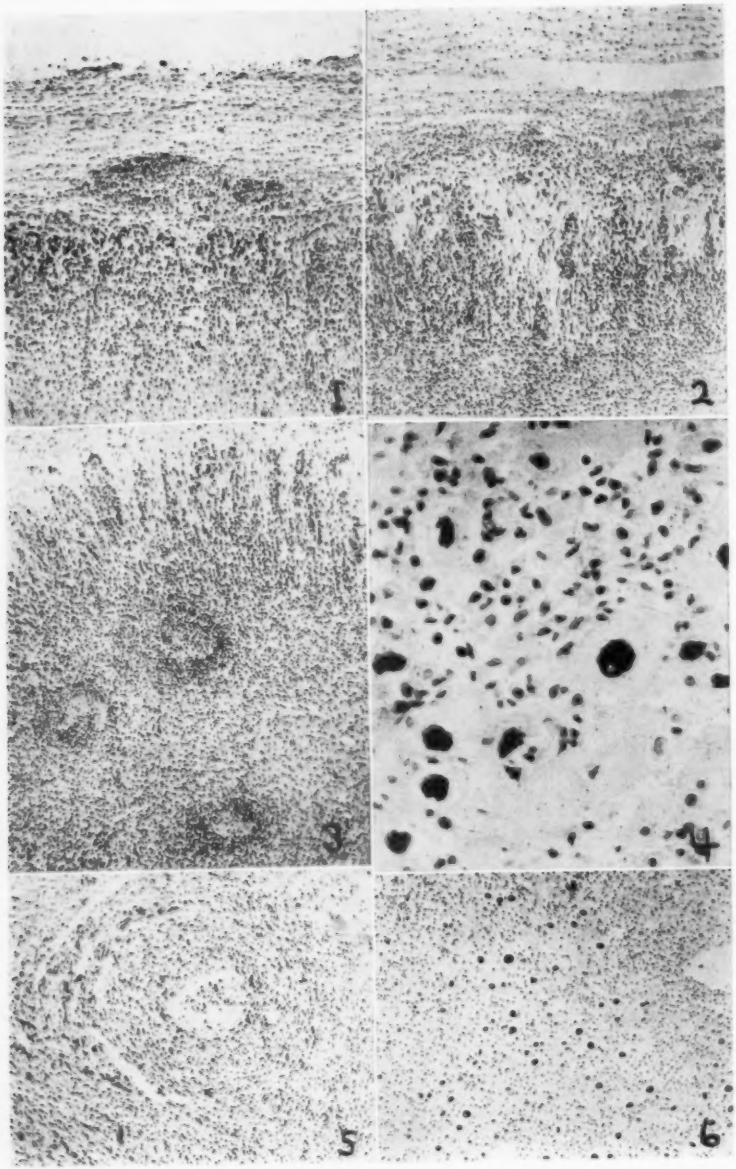
during the first few months of life, naturally contributes some anatomical differences to the picture.

The most common finding has been the occurrence of islands of blood-forming cells in the gland. These may be observed, not uncommonly, also in normal and premature infants during the first few weeks of life, but disappear with age. In non-syphilitic infants the groups of blood-forming cells that we have seen have been rather small, often occurring inside capillaries or attached to the walls of the smallest venules. We have never seen them in non-syphilitic infants in as striking fashion as it has occurred in several of our present cases. In one case there were large masses of immature red blood cells occupying a large part of the outermost layer of the cortex. In another, large masses of myeloid cells were sprinkled throughout the gland. Hickel (14) has described such a case. The blood formation here always goes hand in hand with that in the liver. Ssyssojew (25) has shown that experimental benzol poisoning sets up areas of blood formation in the adrenal gland as elsewhere. This extra-medullary blood formation is apparently, therefore, an expression of prematurity or anemia or both, and its part in congenital syphilis appears to be that of these two factors.

The simplest form of direct injury to the adrenal gland is necrosis. Necroses may play a part in many inflammatory processes here, but we have seen several instances in which this was the only marked change. In one case nearly the entire cortex was involved in an early necrosis; the nuclei appeared as faint shadows and there was no demarcation between the cortical cells, the capillaries being lost in the necrotic areas and the medulla being miraculously spared. There was absolutely no cellular reaction to the necrosis. In another case there were large spherical and oblong coagulation necroses in the cortex extending from the capsule to the medulla, also without leucocytic response, in spite of inflammatory changes in the rest of the organ. Aschoff (1) has described wedge-shaped areas of necrosis extending from the inner layer of the cortex to the capsule. Aschoff, Guleke (8), Kokubo (17) and others have observed isolated spherical necroses like the one described, scattered throughout cortex and medulla. In several of our cases there was marked infiltration of the walls of the blood vessels with leucocytes, but it seems impossible to attribute these necroses to vascular changes. While these small sharply outlined spherical

necroses may occur without cellular reaction, entirely similar necroses are found with cell-free centers, but with numerous fragmented and necrotic nuclei in their margins. We have seen one case in which there were many of these small coagulation necroses in the involuting cortex and medulla surrounded by nuclear fragments, but no normal leucocytes (fig. 3), together with other changes. There is a great variety of distinct and different changes which may go to make up the whole picture in any given instance.

What appears to be by far the most frequent and characteristic lesion of the adrenal gland in congenital syphilis was described by Simmonds (24) and given the name "perihypernephritis syphilitica." We have seen this alteration in twenty-two cases. In the more marked instances it consists of an extraordinary amount of connective tissue in the capsule which is very cellular and contains no collagen fibers (fig. 1). This young connective tissue is seen to consist of many layers of cells, which, in sections, often shrink away from each other. In infants which had lived for several weeks or months this newly formed connective tissue appears denser, but the amount of collagen is not increased and the capsule is yet very cellular. The normal adult adrenal gland has a fairly thick capsule as has the adrenal gland of the adult dog and other animals, but here the capsule contains much dense collagen and very few nuclei, in sharp contrast to the condition in these cases of congenital syphilis. In most instances this connective tissue is projected downward into the cortex between the groups and strands of cortical cells, thus separating them from one another. In two cases we have observed a most remarkable loss of cellular cortical substance between the bundles of connective tissue (fig. 2). There are no necrotic cells to be seen and it is possible that this finding represents a failure of the cortex adequately to develop in the presence of the fibrosis, rather than a destruction of tissue. In such markedly altered capsules necroses are prone to occur. These may appear without cellular reaction, they may be surrounded by leucocytes or they may consist of a mass of necrotic leucocytes. Groups of leucocytes of all varieties without necrosis may be seen and there are usually many wandering cells and plasma cells scattered through such a capsule. Spirochaetes usually occur in great abundance here. This seems to be probably entirely an inflammatory reaction, though it is perhaps



FIGS. 1–6

comparable to the fibrosis which is so often seen in the liver and pancreas, about which there is some dispute.

Other inflammatory changes have been described by various writers, and we have seen them in the cortex and medulla of many of our cases which showed the capsular changes. Leucocytes of all varieties are scattered throughout the gland. Occasionally there are collections of lymphocytes and plasma cells in small groups, particularly in the medulla. In several of our cases there are pigment-laden phagocytes which speak of previous hemorrhage. Paunz (21) has studied the groups of cells which are so often found in the adrenal gland, and shows that in infants groups of sympathogoniocytes are frequent, and that groups of lymphocytes and plasma cells are commonly found where there is no explanation for their presence. The process of post-foetal development serves well to confuse the picture in infants of one or two months of age. In one infant four months of age the medullary part of the gland showed great numbers of single cortical cells intermingled in the low grade inflammatory process, together with a considerable amount of fibrous tissue, so that the medullary part of the gland was broad and thick and really consisted of involuting cortex which was caught in the inflammatory process, with almost no chromaffin cells. Eosinophiles, diffusely scattered, are commonly met with, and in the above case they were present in large numbers. Together with the inflammatory process in the inner parts of the gland there is the production of a varying amount of fibrous tissue, usually rather small,

---

FIG. 1. CORTEX AND CAPSULE SHOWING THICKENING OF CAPSULE AND NECROSIS IN CAPSULE. MALE INFANT, AGED 2 MONTHS. MARKED CONGENITAL SYPHILIS OF OTHER ORGANS, SPIROCHAETES ABUNDANT

FIGS. 2 AND 3. SHOWING CAPSULAR THICKENING, LOSS OF CORTICAL CELLS AND COAGULATION NECROSES. MALE INFANT, AGED 2 MONTHS, MARKED CONGENITAL SYPHILIS OF OTHER ORGANS. SPIROCHAETES ABUNDANT

FIGS. 4 AND 6. INFANT, AGED 20 DAYS. NO SPIROCHAETES. EVIDENCE OF CONGENITAL SYPHILIS IN BONES AND PANCREAS. LARGE CELLS IN MEDULLA

FIG. 6. Low power

FIG. 5. MALE INFANT, AGED 12 DAYS, SPIROCHAETES ABUNDANT. MARKED CONGENITAL SYPHILIS OF OTHER ORGANS. VASCULAR INFILTRATION BY LEUCOCYTES OF CASULAR ARTERIOLE

whence the process has been called a productive inflammation. In one of our subjects, aged one month, the medulla consisted largely of a mass of dense young fibrous tissue, with the remnants of an inflammatory process. In another case (fig. 4) in which there was evidence of congenital syphilis in the other organs, the only thing abnormal seen in the adrenal gland was a great number of large pale cells in the medulla, with clear pale cytoplasm and darkly staining nuclei which apparently consisted of many smaller nuclei closely packed together. It seemed unlikely that these cells had anything to do with syphilis (figs. 4, 6).

In none of these two hundred and fifty cases, nor in some hundred and fifty others which defied microscopy on account of poor preservation, were any macroscopic gummata of the adrenal gland seen. Winogradow (27) reported a gumma of the adrenal gland in a congenitally syphilitic infant three weeks old. Huber (15), Girode (6) and Oberndorfer (20) have reported one case each of gumma of the adrenal gland. Esser (4) reported a remarkable change in the entire adrenal gland which he believed to be gummatous in nature and in which spirochaetes were present. Certain it is that true gummata of the adrenal gland in congenital syphilis are inordinately rare. Microscopic gummata or miliary gummata have been frequently described in the adrenal gland as in other organs, notably the liver. These are the coagulation necroses with cellular response described above. Other writers have included groups of cells without necrosis in this classification, but we believe it better to omit the term entirely.

Of the process of repair of any of these lesions or of any changes in the adrenal gland in late congenital syphilis we have no knowledge.

REFERENCES

(1) Aschoff: Über akute Entzundungsercheinungen an Leber und Nebenniere bei kongenitaler Syphilis. *Ver. d. deut. path. Gesell.*, vi, 1903, 205.

(2) Baerensprung: Die Hereditäre Syphilis, Berlin, 1864.

(3) Dietrich und Siegmund: Die Nebenniere u.s.w. *in* Henke-Lubarsch, Handbuch der spez. path. Anat. u. Hist., Springer, Berlin, 1927, p. 1031.

(4) Esser: Zur Kenntnis der kongenitalen Nebennierenlues u.s.w., *Münch. med Wchnschr.*, iv, 1908, 1170.

(5) Gierke: Das Verhältniss zwischen Spirochaeten und den Organen kongenital syphilitischer Kinder. *Münch. med. Woch.*, liii, 1906, 393.

(6) Girode: Syphilis congenitale. *Bull. d. l. Soc. anat. de Paris*, lxv, 1890, 215.

(7) GOLDZIEHER: The Adrenal Gland, MacMillan, New York, 1929.
(8) GULEKE: Zur Frage des Verhaltens der Nebennieren bei kongenitaler Syphilis. *Virch. Arch.*, clxxiii, 1903, 519.
(9) HECKER, C.: Über Syphilis congenita inneren Organe. *Monatschr. f. Geburtsk. u. Frauenkr.*, xxxiii, 1869, 22.
(10) HECKER, R.: Beiträge zur Hist. u. Path. der congenitalen Syphilis u.s.w., *Deutsch. Arch. f. Klin. Med.*, lxi, 1898, 1.
(11) *Idem:* Die Erkennung der fötalen Syphilis. *Deutsche. med. Wchnschr.*, 1902, 808, 826.
(12) HERXHEIMER: Der path. Anat. der congenitalen Syphilis. *Ergeb. der allg. Path.*, xii, 1908, 144.
(13) HERXHEIMER: Über die path. Anat. der kongenitalen Lues., *Ver. d. deut. path. Gesell.*, xxiii, 1928, 144.
(14) HICKEL: Hemopoiesie dans la cortico-surrénale d'un nouveau-né hérèdo-syphilitique. *Comp. rend. Soc. Biol.*, lxxxiv, 1921, 676.
(15) HUBER: Einige Notizen über Erkrankungen der Nebennieren bei kongenitalen Syphilis. *Deutsch. Arch. f. klin. Med.*, v, 1869, 5.
(16) JUMBO: Über die Nebenniere bei angeborener Syphilis. *Ver d. jap. path. Gesell.*, ix, 1919, 59.
(17) KOKUBO: Über die congenitale Syphilis der Nebennieren. *Ztbl. f. allg. Path.*, xiv, 1903, 666.
(18) LEWIS AND PAPPENHEIMER: *Jour. Med. Research*, xxxiv, 1916, 81.
(19) NEUSSER UND WIESEL: Die Erkrankungen der Nebenniere, Holder, Leipzig, 1920.
(20) OBERNDORFER: Über die viscerale Form der congenitalen Syphilis u.s.w. *Virch. Arch.*, clix, 1900, 179.
(21) PAUNZ: Über die Rundzellenherde der Nebenniere. *Ibid.*, ccxlii, 1923, 138.
(22) RIBADEAU-DUMAS ET PATER: *Arch. de Méd.*, xxi, 1909, 154.
(23) SHIOMI: Über die extramedulläre Blutbildung bei Lues congenita. *Ver. d. jap. path. Gesell.*, viii, 1919, 94.
(24) SIMMONDS: Die Nebenniere bei Syphilis congenita. *Virch. Arch.*, ccxviii, 1914, 152.
(25) SSSYSOJEW: Über Blutbildumg in der Nebenniere. *Ibid.*, ccxlvi 1923, 259.
(26) VIRCHOW: Über die Natur der constitutionell-syphilitischen Affectionen. *Ibid.*, xv, 1858, 217.
(27) WINOGRADOW: Ein Fall von kalziniertem Gumma der Nebennieren bei Syphilis congenita, *Ergeb. d. allg. Path.*, v, 1898, 650.

THE CELLS FOUND IN TUBERCULOUS TISSUES AS DEMONSTRATED BY VITAL AND SUPRAVITAL STAINING[1,2]

EDNA H. TOMPKINS AND R. S. CUNNINGHAM

From the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee

Analysis of the findings reported from experiments, in which tuberculous tissues have been stained vitally or supravitally, leads to the conclusion that the masses of large mononuclear cells, which are difficult to distinguish in fixed sections, are composed of cells which react to vital or supravital dyes in a variety of different ways.

Goldmann (4) (5) and Kiyono (7) found that the large mononuclear cells of the connective tissues of normal animals, which had been given vital dyes, always contained the stains in characteristic deposits. They also found that a great number of the large mononuclear cells in a tuberculous area from a vitally stained animal contained the dyes in types of deposition foreign to normal tissue, or showed no vestige of them. Goldmann stained tuberculous mice vitally with pyrrol blue, isamin blue and trypan blue. He found that the vitally stained macrophages ingested the bacilli of avian tuberculosis, and showed changes which indicated transitions from large deposits of dye into fine granules of the stain, and then into a diffuse coloring. Finally, all vital dye disappeared from the cells. At this stage bodies appeared which took fat stains, and soon thereafter the cells disintegrated. In definite tubercles, Goldmann (5) found that these changes occurred in more or less specific bands. At the center of the tubercle there were mononuclear cells without vital stain, but with nuclei which appeared normal. Surrounding these cells were others of the same size, which were diffusely colored by the vital dye. Outside of this zone of diffusely stained cells were cells with small discrete granules of the stain.

[1] This work was assisted by a grant from the Research Committee of the National Tuberculosis Association.

[2] Submitted for publication August 2, 1930.

Finally, on the periphery of the tubercle, there were vitally stained cells of the type which Goldmann found in all normal connective tissue, and in the spleen, bone marrow and liver.

Kiyono stained tuberculous rabbits vitally with carmine. His descriptions of the tissues are very similar to those of Goldmann. In areas where there was much fibrous tissue, he found that the fibroblasts joined in the formation of the tubercle, and passed through a process of gradual loss of the dye similar to that observed in the macrophages.

Evans, Bowman and Winternitz (3) injected rabbits intravenously with trypan blue and bovine bacilli. They found that early in the infection the Kupffer cells of the liver took part in the reaction, and that the normal, massive deposits of the vital dye within them became changed into a diffuse staining. They also found that giant cells developed from the endothelial cells of the liver and contained the vital dye. Later in the course of the infection, unstained mononuclear cells appeared in the areas of invasion.

In the supravitally stained scrapings from tuberculous lesions Cunningham, Sabin, Sugiyama and Kindwall (2) found not only the cell which they defined morphologically as the epithelioid cell, but also large numbers of monocytes and unstained cells, which they identified as reticular cells. Cash (1) developed a method by which the tissues could be stained supravitally and fixed *in situ* immediately after death. By this method he identified monocytes and epithelioid cells in tubercles. At the same time he demonstrated the presence of large mononuclear cells containing massive deposits of the dye which were so extensive that they often covered the nucleus. The type of staining described in these cells corresponds to that of macrophages when exposed to neutral red.

The etiology of the epithelioid cell, and its relationships to the other mononuclear cells in tuberculous tissues, and to the normal connective-tissue cells, are largely questions of conjecture. Cunningham, Sabin, Sugiyama and Kindwall consider that the epithelioid cell is derived from the monocyte. They base their conclusions on the presence of great numbers of monocytes in scrapings from tuberculous tissues, and on the various transitional types which can be found between the monocyte and the epithelioid cell. Most of the workers with vital dye consider that the epithelioid cell, as defined in the less

specific and more general sense of the large mononuclear cell of tuberculous tissues, arises from the large phagocytic cell of the connective tissues. They base their decision principally upon two observations. First, they found the bacilli in stained cells. Second, they could follow transitions in the staining in tubercles, which began with the normal large phagocytic cell filled with the particular vital dye which had been employed, and continued through a series of cells with less and less stain to the unstained large mononuclear cell, which they always found toward the center of the tubercle.

Up to the present, correlation has not been made between the cells in vitally stained tuberculous tissues and the cells which stain characteristically with neutral red in supravital preparations of scrapings from tuberculous areas. In the work reported here, we have combined the methods of fixed, vital and supravital staining in the study of tuberculous tissues in order to determine the relationship between the vitally stained cells in the tissues and those which stain supravitally with neutral red.

The experiments may be separated into two groups. These represent, respectively, studies of chronic tuberculosis in animals given trypan blue after the infection had been present for some time; and studies of early tuberculosis in animals, which had been vitally stained previous to inoculation. In the first group, twelve guinea-pigs were given intraperitoneal inoculations of human tubercle bacilli (strain 573, obtained from the American Type Culture Collection). Six weeks later intraperitoneal injections of 2 to 3 cubic centimeters of a 1 per cent solution of trypan blue in distilled water were started. The dye was given on alternate days until the animals were well stained, or until they were sacrificed for some especial reason. The animals were sacrificed for study at intervals varying from 2 to 64 days after vital staining had been begun. In the second group, twenty guinea-pigs were subjected to a prolonged course of vital staining with trypan blue until their tissues were deeply stained. They were then given inoculations of heavy suspensions of viable human tubercle bacilli in a mesenteric vein, nine receiving strain 573, and eleven receiving strain 571. The intraperitoneal injections of trypan blue were stopped for three days following the inoculations, and were then continued every other day until the animal was sacrificed. These animals were killed for study at intervals varying from two to forty-six days after inoculation.

At the time of autopsy, supravital studies were made of scrapings from the lungs, livers, spleens, lymph nodes and at times of peritoneal exudates and omental spreads. The supravital preparations were made in the usual manner. Tissues from the same organs were fixed in 10 per cent neutral formalin, in the case of the animals inoculated with strain 573; and in the solution of bichloride in acetic alcohol and chloroform recommended by Hetherington and Tompkins (6) in the case of the animals inoculated with strain 571. The tissues were embedded in paraffin after both methods of fixation. Sections of these fixed tissues were stained with carmine, with hematoxylin and eosin, or with carbol fuchsin for tubercle bacilli. Comparison of the fresh smears with the tissues fixed in formalin showed that a variable amount of the vital dye was always extracted from the cells during the process of fixation and dehydration. This was not true in the case of the tissues fixed in the modified solution of Carnoy and Lebrun. With that fixative, however, some cellular distortion was occasionally found.

EXPERIMENTAL OBSERVATIONS

It is well at this point to describe the variations in color found in the supravitally stained cells of the scrapings made from these experiments, since many of the cells contained more or less trypan blue in addition to the neutral red. The neutral red entered the same areas in the cells as were occupied by the trypan blue. The resulting color of the vacuoles, therefore, depended upon the relative amounts of the two dyes present, and varied from blue without red, through various shades of purple, to the color of neutral red without any underlying blue. There were border-line cases in which the amount of blue was so faint, and the amount of red so great, that the presence of blue was noted only at the edge of the vacuole. In the instances in which it was difficult to detect the blue, the color could usually be ascertained by examination of the unstained slide, where faintly stained cells were easily seen. In the following discussion of the types of staining found in the supravital scrapings, statement of the absence or presence of either of the dyes has usually been based upon an evaluation of the various combinations of red and blue in the cells on the stained slide.

The number of the cells present in the supravitally stained scrapings of the tissues varied somewhat from animal to animal, but the types of

staining observed were sufficiently consistent throughout the series for very definite generalizations to be permissible. The majority of the cells in all of the scrapings, exclusive of the parenchymal cells, consisted of large mononuclears. There were always a few small mononuclear cells of 12 microns in diameter, or less, which never contained trypan blue, but which at times contained a drop or so of neutral red. Janus green revealed a considerable number of moderately long, thick, rod-shaped mitochondria close to the nucleus. These cells, therefore, stained in the manner characteristic of the lymphocytes of the circulating blood, and were considered to be normal lymphocytes.

There were likewise a moderate number of polymorphonuclear leucocytes. They usually contained a few highly refractive, unstained droplets in the cytoplasm, and, at times, also a vacuole or so stained with neutral red. Very rarely, on the plain slide, they showed a drop or two of trypan blue. This was so faint as to have been obscured by the supravital stain.

There were always great numbers of monocytes containing neutral red and janus green arranged as described by Sabin, Doan and Cunningham (8) (Figs. 1 a, 1 b). The average diameter of these cells was about 12 microns. Many of these cells were binucleated, and the nuclei rarely contained nucleoli. The vacuoles of neutral red in the rosette were graduated in size from very fine ones in the center to droplets of about one micron at the periphery. Very rarely they had a faint purple tint, as is shown in figure 1b. This was usually so faint that it was only shown by a darkening at the periphery. The cells on the unstained slides which had the same dimensions, and were seen to contain vacuoles in similar arrangement, confirmed the presence of a faint amount of blue in the vacuoles. The numbers of these cells which contained blue on the plain slides were, however, considerably less than the numbers which took neutral red on the stained slide. In other words, the monocyte exhibited an active capacity to stain supravitally with neutral red, but a very limited ability to take up trypan blue. When found in scrapings from the lungs, it frequently contained particles of carbon scattered throughout the rosette.

There were always great numbers of large mononuclear cells which in every respect were similar to the vitally stained clasmatocytes, or macrophages, of the connective tissues (Fig. 2). These large phago-

cytic cells in connective tissues have been called by various names, only a few of which need be mentioned here. The most familiar of these names are the adventitial cell, the pyrrol cell, the histiocyte, the resting wandering cell, and the endothelial phagocyte. The term clasmatocyte has been used most often in the literature for this specific cell and it is the term which we shall use here. This cell was about twenty or more microns in diameter. At times a definite, clear contracted zone could be seen on the periphery; including this zone, when visible, the total size of the cell was as much as 32 microns. Usually the peripheral transparent areola was not visible. Compared to the amount of cytoplasm, the nucleus was relatively small; it was about the size of that in the monocyte, and it frequently contained nucleoli. A few of these cells were bi-nucleated. The staining of the cells was characteristic. Both dyes were deposited together in massive amounts in vacuoles of all sizes, which were scattered throughout the cytoplasm. On the unstained slides the vacuoles were dark blue in color. In the scrapings from the lungs, these cells frequently contained large amounts of carbon scattered among the vacuoles of dye. (The solid black deposits in the illustrations represent inclusions of carbon which were present in the cells.) Cells of this type were seen at times to contain great numbers of rods, which were much larger than the mitochondria, and which usually stained a deep blue, but were at times unstained and highly refractive. These rods were most frequently arranged radially with the end of each rod directed toward the nucleus. The clasmatocytes occurred in greatest numbers in the scrapings from the spleens, but were likewise present in varying amounts in the scrapings from the lymph nodes and livers. At times, they occurred in tremendous numbers in the scrapings from the lungs, and in many instances they were the predominating type of cell. At other times, the clasmatocytes were less frequent in the scrapings from the lungs, and were supplanted to greater or lesser degree by epithelioid cells. In the scrapings from the chronic infections, but less rarely in those from acute infections, there were many cells which were entirely similar in staining characteristics to the epithelioid cell as described by Cunningham, Sabin, Sugiyama and Kindwall. These cells varied in size from one slightly smaller than the average clasmatocyte (20 microns) to one of much greater diameter (Figs. 3a, 3b, 3c). They usually

contained one to two nuclei, which often had nucleoli. They were never seen with a transparent, undulating membrane about the periphery similar to the membrane observed in the clasmatocytes. These cells always, however, showed a clear peripheral zone of cytoplasm in which there was never any dye, but which often contained refractive droplets. Although usually as large, or larger than those of the monocytes, the nuclei of these cells were small compared to the amount of cytoplasm. The dye in the cells was segregated into innumerable fine vacuoles which were very even in size and which were collected into a large rosette about a small, clear area in the hof of the nucleus. The neutral red in the vacuoles of these cells was fainter in color than in those of the monocytes. It was usually of the same hue as in the monocytes, but at times it was a slightly deeper red. In about fifty per cent of these cells there was a tint of blue, which gave a lilac hue to the vacuoles when stained with neutral red. Figure 3c represents a cell in which the vacuoles contained blue. On the unstained slide some of the cells contained pale blue rosettes. The blue tended to stain the rosettes more diffusely than did the neutral red. Nevertheless, in general, each rosette was very definite, and occupied only the part of the cytoplasm within the hof of the nucleus. It is probable that this diffuse staining was due to the ultra-microscopic size of the particles of blue. As was true in the case of the monocytes, the number of these cells which contained blue on the plain slide was much less than the number which had taken neutral red on the stained slide. Undoubtedly, in the latter case, traces of blue were obscured by the neutral red in many instances, but still it is obvious that many of these cells which stained supravitally did not contain the vital dye. In the periphery of the cells there were often a few, fine, unstained, highly refractive droplets. At times the cells contained rod-shaped bodies which stained readily, which were usually highly refractive, which were much larger than the mitochondria, and which had a spoke-like arrangement in the rosette with the centriole as the hub. The cells from the lungs usually contained, in addition to the neutral red and trypan blue, many fine particles of carbon scattered throughout the rosette. While the particles of carbon were, on the average, smaller than those seen in the clasmatocytes and monocytes, they were usually larger than the deposits of neutral red. Figure 3b represents an epi-

thelioid cell which contained considerable carbon. Epithelioid cells both with and without blue were found in the scrapings from all of the tissues of the more chronically infected animals, but they were more constant, and occurred in greater proportions in the scrapings from the lungs than in those from the other organs. In the scrapings from the earlier infections, on the other hand, which resulted from the inoculations in the mesenteric veins, monocytes were the predominant mononuclear cell and epithelioid cells were relatively infrequent. Epithelioid cells containing blue were particularly infrequent. As the duration of the infection increased, however, the numbers of epithelioid cells definitely multiplied, and there was a corresponding increase in the number of them which contained blue rosettes.

Besides these three specific types of cells, there were many cells in the scrapings in which the manner of staining presented mixtures and modifications of the three specific types.

There could always be found cells with characteristics of both monocytes and epithelioid cells. These were wholly similar to the transitional forms between monocytes and epithelioid cells described by Cunningham, Sabin, Sugiyama and Kindwall. In the scrapings from the earlier infections these cells, together with monocytes, formed by far the greatest numbers of the large mononuclear cells present. These cells were as large as, or larger than, monocytes, but usually smaller than the epithelioid cells. Like the monocytes, few of them contained blue, although they all showed well stained rosettes of neutral red. The vacuoles of neutral red tended to be more even in size, and smaller, on the average, than those of the monocyte. These characteristics were more pronounced in the larger cells. Figure 4 represents this type of cell. The cell shown in figure 3a probably developed from a cell of this type. There were at times a few highly refractive, unstained droplets in the peripheral part of these cells.

Besides the cells described above, there were also many cells which exhibited mixtures, in varying proportions, of the characteristics in staining of both the clasmatocyte and epithelioid cells. Some of the cells were more like one, and some more like the other. These cells were found more frequently in the scrapings from the older infections than in those from the younger ones, and they were more commonly seen in the scrapings from the lungs than from any other organ.

Figures 5a and 5b represent cells of this type. These mixed forms were usually of the same size as the clasmatocytes and epithelioid cells: that is, they averaged 20 microns in diameter. They showed no clear peripheral zone. In general, they contained one to two nuclei, often with nucleoli. The cells contained definite rosettes which were usually composed of both dyes arranged about a centriole in the hof of the nucleus (Fig. 5a). The vacuoles in the rosettes were deeper in color, and were larger and more irregular in shape than those found in the epithelioid cells; at the same time they were lighter in color, smaller and more even in size than the vacuoles found in the clasmatocytes. The color of the different deposits in the individual cell often varied somewhat in intensity. As has already been emphasized, there were many variations in this type of cell. In some the rosette was composed almost entirely of fine, very even deposits with only an occasional large vacuole (Fig. 5b). In others, the deposits were fairly even in size, but were definitely larger than those of the monocyte (Fig. 5a). Some of the cells were indistinguishable from clasmatocytes, which had rounded up and had their vacuoles arranged in rosettes. In scrapings from the lungs, cells of this type frequently contained particles of carbon which were arranged in the same general manner as the blue and red dyes. At times this type of cell was seen to contain stained and unstained bacilli.

These cells apparently were transitions between clasmatocytes and epithelioid cells. This deduction that epithelioid cells are formed from clasmatocytes is based upon the same line of reasoning as that employed in following the origin of epithelioid cells from monocytes. It is based upon a series of transitional forms. It has, however, one added factor of evidence. Not only were there transitions in the manner of staining with the supravital dye, but there was also a series of transitions to be observed in the storage of the vital dye. Indeed, in view of the fact that monocytes were rarely found with any but the faintest traces of the vital dye, it is difficult to explain the presence of the blue in the epithelioid cells, in which it occurred, on any other premise than that they developed from the vitally stained clasmatocytes. It thus becomes evident that, while the epithelioid cells which did not contain blue may all have come from monocytes, those, at least, which contained blue, must have come from cells which originally stored the vital dye.

Besides the stained cells in the scrapings, there were always great numbers of large mononuclear cells which did not stain with either the vital or supravital dyes (Figs. 7a, 7b). The identity of these unstained mononuclear cells could not be definitely determined, but in view of the fact that there were always many cells which still contained some of the dyes, but were definitely in progress of degeneration, it is probable that these unstained cells were simply end results of this process. Figure 6 represents a degenerating cell of this partly stained type. The dyes occurred in these degenerating cells as faint splotches of color, in contradistinction to the discrete deposits which occurred in the monocytes, clasmatocytes and epithelioid cells. The color of these splotches varied in shade from lilac to pure red or pure blue, and the number of the splotches varied from a few, scattered here and there in any part of the cytoplasm, to a single red or blue area in the hof of the nucleus. The cells shown in figures 2, 6 and 7a, in sequence, were transitions in the process of degeneration leading to completely unstained (dead) cells.

In the scrapings from the older infections there were usually to be found multinucleated or giant cells. Figures 8a, 8b, 8c and 8d represent varieties of giant cells which were frequently seen. The giant cells usually measured 32 or more microns in diameter, and contained many nuclei. Usually some of the nuclei in a cell showed nucleoli and some did not. The nuclei were round or oval in shape, and might be either closely adjacent to each other, or variously spaced within the cell. They were usually near the periphery of the cell, but at times cells were also found with the nuclei half way between center and periphery, or even at the center. Usually these giant cells contained variable numbers of scattered, unstained droplets of high refractivity, which took fat soluble stains. The deposits of vital and supravital dyes within the cells were comparable to the different types of deposits observed in the mononuclear cells The staining was at times similar to that observed in the clasmatocytes (Fig. 8a), in the epithelioid cells (Fig. 8c), in the transitional forms between clasmatocytes and epithelioid cells (Fig. 8b), and in the degenerating cells. Finally, there were great numbers of giant cells in which no dye was found (Fig. 8d). In the scrapings from the lungs, both the stained and unstained multinucleated cells frequently contained carbon, while bacilli were seen only in the stained cells.

The fixed sections, stained with hematoxylin and eosin, were used merely as a control in estimating the extent, type and arrangement of the tuberculous involvement. Sections from the more chronically infected animals demonstrated the widespread character of the tuberculous involvement in all of the viscera. In the earlier infections, the pathology varied from a few scattered mononuclear infiltrations in the liver, mingled with polymorphonuclear cells, to extensive involvement of the viscera comparable to that in the chronic infections. The degree of involvement paralleled the duration of life after inoculation.

The study of the sections fixed in formalin or in the solutions of bichloride in acetic alcohol and chloroform gave information concerning the position and number of the blue-containing cells. It did not give information concerning the capacity of these cells to stain supravitally at the time of fixation. However, by comparison with the findings in the supravitally stained preparations, it was possible to draw analogies between the various types of blue-containing cells in the fixed tissues, and similar types of cells, which stained with neutral red supravitally. In this way, it was possible to define the localization of typical classmatocytes and epithelioid cells in tuberculous tissue, and to establish the position of the mixed types in the same areas. The small areas of large mononuclear infiltration usually consisted of heavily stained clasmatocytes in the case of the more chronic infections, and of unstained cells in the case of the earlier infections. The larger accumulations of mononuclear cells formed either definite tubercles, or massive infiltrations. Only a variable proportion of the cells in these larger accumulations contained blue; many of these were clasmatocytes. Monocytes could not be definitely distinguished. Rarely a cell was seen with a small, blue rosette similar in character to the blue rosettes at times found in monocytes in the supravital preparations. There were many cells with rosettes composed of very fine, discrete particles of the dye, and others with rosettes in which the dye appeared as a diffuse stain. The cells with these blue rosettes were entirely similar to the blue-containing epithelioid cells in the supravital preparations. Frequently, merely a diffuse blue staining of the entire cytoplasm was observed. The larger number of cells found in the lesions, however, contained no blue stain at all. Scattered among the masses of large mononuclear cells were multinucleated cells. Many of

these showed none of the vital dye, but many were stained in the same variety of ways found in the mononuclear cells in the sections. Where the infiltrations of large mononuclear cells were arranged in tubercles, the centers of the tubercles consisted either of mononuclear cells without stain, or of areas of necrosis diffusely stained with blue. Many large, unstained mononuclear cells were arranged about these areas of necrosis. Next to these cells were layers of cells in which the blue was evident, either by a diffuse staining of the entire cytoplasm, or by the presence of a rosette, in which the dye varied from a diffuse stain to large and small droplets. The cells with the rosettes were similar to the blue-containing epithelioid cells seen in the supravital preparations. Surrounding these cells, which contained relatively small amounts of the stain, were masses of typical, heavily stained clasmatocytes. Cells with blue arranged as in monocytes were never found in the definite tubercles, although they were seen from time to time in the areas of massive, but loose, infiltration.

The polymorphonuclear cells, which appeared in the tuberculous areas, frequently showed definite staining of the specific granules. None were found with large masses of the blue. Many were also found with no staining of the specific granules; but where the granules were stained, they were of a bright blue color, which was more azure than the navy blue of the clasmatocytes.

On the basis, then, of the supravital preparations, and the fixed tissues of these vitally stained animals, it was found that the mass of the large mononuclear cells composing the tuberculous areas consisted of a number of varieties. There were monocytes, clasmatocytes and epithelioid cells, as well as many degenerating cells of these three types, and giant cells, which, by their manner of storing the two dyes, gave evidence of having developed from the various types of mononuclear cells. The monocytes rarely contained the vital dye, while the clasmatocytes stored great quantities of it. The epithelioid cells were found both with and without the vital dye. Transitions could be traced, not only between the monocyte and the epithelioid cell, but also between the clasmatocyte and the epithelioid cell.

In these experiments, both monocytes and clasmatocytes were present in numbers in excess of the normal. Under the influence of the infection, each exhibited changes which resulted in modified forms,

which more and more departed from the original cellular types and partook of the characteristics of the same final type, that of the epithelioid cell. Whether the influence at work to produce these changes acted from without, or from within the cells, can not be determined from these experiments. Both the monocytes and the clasmatocytes were frequently seen to contain bacilli. It seems very likely that the organisms were, therefore, the causative factor of the changes, and worked from within the cells to produce modifications of such a nature that both types of cells assumed similar characteristics, and became the typical epithelioid cells found universally in tuberculous tissues. Both of these cells were actively phagocytic in their normal state, the clasmatocyte being more so than the monocyte. The changes in the size of their cytoplasmic vacuoles, the lessening in intensity of the color of the dyes in these vacuoles, the appearance of fat, the abnormal cellular divisions which resulted in the formation of giant cells, and the final death of the cells with failure to stain, all indicate both lessened phagocytic capacity of the cells, and other degenerative processes. It would seem, therefore, that factors are at work in tuberculosis, which cause an increased production of both monocytes and clasmatocytes, but which so affect these cells that their normal functions are depressed, their normal life cycle becomes perverted, and their normal morphology modified.

We wish to express our appreciation to Miss Susan Wilkes, staff artist, for making the illustrations. These studies necessitated many preliminary drawings of preparations obtained at the time of autopsy.

SUMMARY

Tuberculous guinea-pigs were stained vitally with trypan blue. The tissues were examined both by sections of fixed material and by scrapings stained supravitally.

The large mononuclear cells found in the tuberculous areas consisted of monocytes, clasmatocytes and epithelioid cells, together with transitional and degenerate forms of the same cells. Only a few of the monocytes contained trypan blue, although they stained vigorously with neutral red. The clasmatocytes always contained trypan blue in great amounts. The number of epithelioid cells which contained the vital dye, and the amount of dye within them, varied considerably.

By means of the superimposition of the supravital upon the vital dye, transitions could be followed from clasmatocytes to epithelioid cells, as well as from monocytes to epithelioid cells.

The types of staining observed in the giant cells were analogous to those observed in the mononuclear cells.

The concept has been developed that, in tuberculosis, some toxic factor, acting either from within or from without the cells, affects the functions of both the monocytes and clasmatocytes, so that these cells become modified both in morphology and in activity, and develop into characteristic epithelioid cells, or into giant cells, or die and degenerate at any stage in the course of these changes.

REFERENCES

(1) CASH, J. R.: Vital staining characteristics of the epithelioid cell in experimental tuberculosis. *Proc. Soc. Exper. Biol. & Med.*, 1926–27, xxiv, 193.

(2) CUNNINGHAM, R. S., SABIN, F. R., SUGIYAMA, S. AND J. A. KINDWALL: Rôle of the monocyte in tuberculosis. *Johns Hopkins Hosp. Bull.*, 1925, xxxvii, 231.

(3) EVANS, HERBERT M., BOWMAN, FRED B. AND M. C. WINTERNITZ: An experimental study of the histogenesis of the miliary tubercle in vitally stained rabbits. *Jour. Exper. Med.*, 1914, xix, 282.

(4) GOLDMANN, EDWIN E.: On a new method of examining normal and diseased tissues by means of intra-vitam staining. *Proc. Royal Soc.*, London, Series B., 1912, lxxxv, 146.

(5) GOLDMANN, EDWIN E.: Neue Untersuchungen über die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung." H. Laupp, Tübingen, 1912, pp. 108.

(6) HETHERINGTON, DUNCAN C. AND EDNA H. TOMPKINS: The fixation of tissues vitally stained with trypan blue. (*In press.*)

(7) KIYONO, K.: Die vitale Karminspeicherung. Gustav Fischer, Jena, 1914, pp. 258.

(8) SABIN, F. R., DOAN, C. A. AND R. S. CUNNINGHAM: Discrimination of two types of phagocytic cells in the connective tissues by the supravital technique. *Contrib. to Embryol.*, 1925, xvi, 125.

DESCRIPTION OF PLATE

PLATE 1

All of the figures on this plate represent cells stained with neutral red in supravital scrapings from tuberculous guinea-pigs which had been previously stained vitally with trypan blue. All of the cells were drawn to the same scale, ×750. Figure 9 represents a red cell for comparison. Black inclusions in the cells represent carbon. Purple inclusions represent mixtures of trypan blue and neutral red. Red inclusions represent deposits of neutral red only.

FIG. 1A. A monocyte in which no trypan blue was present.

FIG. 1B. A monocyte which contained a trace of trypan blue.

FIG. 2. A clasmatocyte containing both dyes and a few particles of carbon.

FIG. 3A. A small epithelioid cell which did not contain trypan blue. This cell probably developed from a cell similar to that shown in Figure 4, which in turn probably developed from a monocyte.

FIG. 3B. An epithelioid cell larger than the one shown in Figure 3A. This also contained no trypan blue but had considerable carbon in its rosette.

FIG. 3C. An epithelioid cell which contained trypan blue as well as neutral red. This probably developed from a cell like that shown in Figure 5A, which in turn probably came from a clasmatocyte of the character shown in Figure 2.

FIG. 4. A cell without trypan blue but with considerable neutral red. It probably represents a transitional stage between a monocyte (Fig. 1A) and an epithelioid cell (Fig. 3A).

FIG. 5A. This cell contained both dyes in moderate-sized deposits in a rosette and was probably a transitional form between a clasmatocyte (FIG. 2) and an epithelioid cell (Fig. 3C).

FIG. 5B. This cell was very like the cell shown in Figure 5A and was also probably transitional between a clasmatocyte (Fig. 2) and an epithelioid cell (Fig. 3C).

FIG. 6. This cell contained very little trypan blue. The deposits of neutral red had become conglomerate. The cell was probably a transitional form between a heavily stained clasmatocyte (Fig. 2) and a dead and unstained cell (Figs. 7A, 7B).

FIG. 7A. This cell contained no trypan blue and was unable to take the neutral red. It was a dead cell. It contained bodies of low refractivity. It was probably a clasmatocyte and had come from a cell similar to that shown in Figure 6, which in turn represented a stage in the degenerative process leading to death.

FIG. 7B. This was a cell very like that shown in Figure 7A. It had simply degenerated further than that cell and had lost the unstained bodies which were present in that cell.

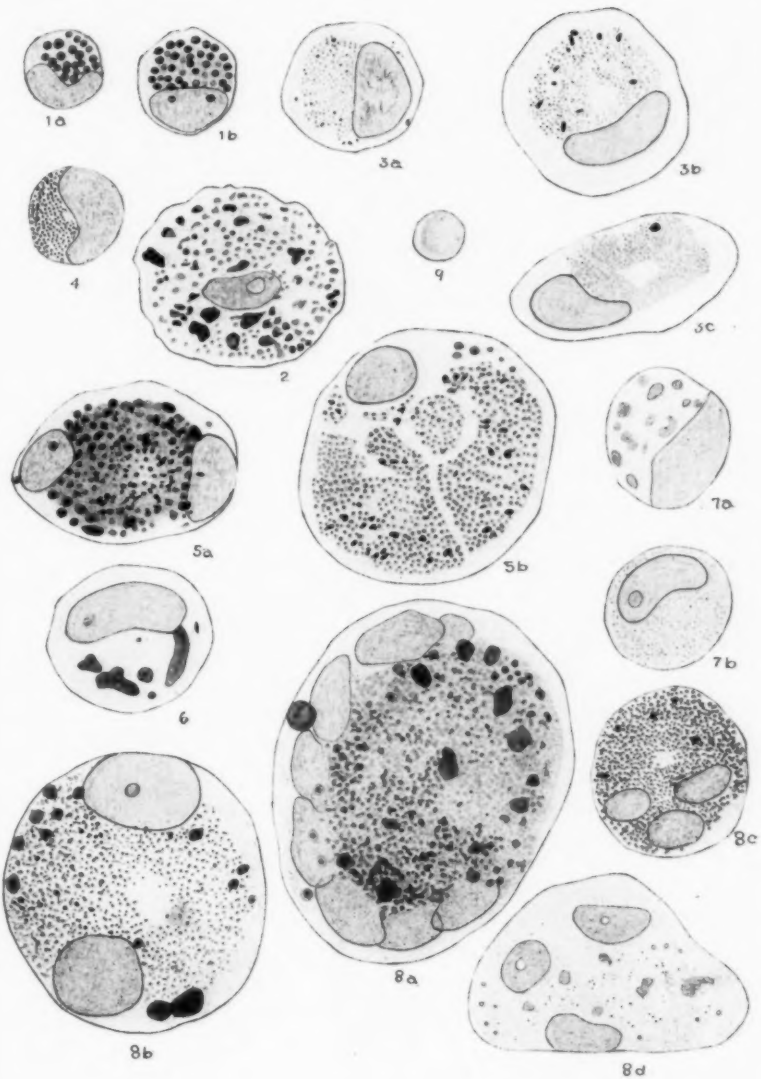
FIG. 8A. (A giant cell with peripheral nuclei. It contained large amounts of both dyes arranged as in a clasmatocyte (Fig. 2).

FIG. 8B. A giant cell which contained very little trypan blue but considerable neutral red. The dyes were arranged in a rosette in a manner which suggested the type of deposit seen in the mononuclear cells of type V (Fig. 5A); that is, in large and small-sized vacuoles half way in size between those of the clasmatocyte and those of the epithelioid cell.

FIG. 8C. A giant cell with a rosette typical of that in the epithelioid cell, such as that shown in Figure 3B. Carbon was also present in the cell, but trypan blue was absent.

FIG. 8D. A giant cell which had lost the ability to stain, but which showed bodies of low refractivity in its cytoplasm such as were seen in the mononuclear cell shown in Figure 7A.

FIG. 9. A red blood cell drawn to scale for comparison with the mononuclear cells illustrated above.


1a
1b
3a
3b
4
2
9
3c
5a
5b
7a
6
7b
8a
8c
8b
8d

DI-HYDRANOL

Control of Intestinal Putrefaction in Man by Oral Administration of 2-4-dihydroxyphenyl n-heptane[1]

VEADER LEONARD, M.D. and WILLIAM A. FEIRER, M.D.

From the Department of Bacteriology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland

It has been generally supposed that the hydrolysis of protein by putrefactive organisms in the human intestine is a process which is constantly present under ordinary conditions of climate and diet. Some of the end products of putrefaction are usually considered to be more toxic than either those of tryptic digestion or those resulting from bacterial decomposition of carbohydrate material by fermentation. For this reason the putrefactive organisms of the intestinal tract have been held to be responsible, by many, for various clinical conditions supposed to arise from absorption of these toxic products.

A large literature on this subject has accumulated during the past thirty years, and has furnished some of the bitterest controversies in modern medicine. A discussion of the subject by the Royal Society of Medicine (1) in 1913 covers 360 pages. In a review published in 1924 Alvarez (2) quotes 254 references. Schieblisch (3) has recently reviewed the experimental literature.

The proponents of the theory of intestinal toxemia as a fruitful cause of disease base their argument on the clinical success of measures calculated to inhibit intestinal putrefaction. Their opponents, defending a much simpler position, base their objection to this theory on the fact that no one has been able to furnish satisfactory experimental evidence in support of it. Neither group appears to have questioned the universal presence of true putrefaction in the human intestine in spite of the fact that convincing proof of this idea is peculiarly difficult to find.

It is not the purpose of this paper to enter this clinical controversy.

[1] Submitted for publication October 13, 1930.

It is rather its purpose to present experimental evidence in support of two conclusions, both of which were unexpected:

1. That intestinal putrefaction[2] in man is not nearly so universal and constant a process as has been generally supposed.

2. That the putrefactive flora of the intestine can be completely eliminated by oral administration of 2-4-dihydroxyphenyl n-heptane, a synthetic substance for which we propose the contraction—*dihydranol.*

DETERMINATION OF THE PRESENCE OR ABSENCE OF INTESTINAL PUTREFACTION AND ITS QUANTITATIVE ESTIMATION

Attempts have been made to estimate the degree of intestinal putrefaction by indirect chemical means such as the notoriously inaccurate indican test in its numerous modifications, and more recently by Bergheim (4) (5) (6), who regards the percentage reduction of ferric oxide in its passage through the alimentary canal as a measure of intestinal putrefaction and has described an ingenious method for its determination.

There are but two species of organisms generally recognized as being largely responsible for true putrefaction in the human intestine. They have been named *Clostridium sporogenes* and *Clostridium putrificum.* Both are Gram-positive, obligate anaërobes, and both are spore formers. They grow readily in Holman's cooked meat media (7) under anaërobic conditions and when present in the feces, their isolation and identification offer no great difficulty.

It is apparent that if either or both of these organisms are present in the intestinal contents in sufficient numbers to set up putrefactive processes active enough to be of any probable clinical significance, the stools would surely contain their spores.

The presence or absence of true intestinal putrefaction in any given case may therefore be determined by direct bacteriological methods. Furthermore, the relative degree of intestinal putrefaction, as measured by the number of putrefactive organisms in the stool, may be

[2] Throughout this paper the writers follow the position of von Hibler and Rettger on true putrefaction—namely, the breaking down of proteid material by microorganisms with the production of odors characteristic of cadaveric decomposition.

determined by making up a known emulsion of the stool and inoculating a series of tubes of cooked meat with a definite quantity (1 cc.) of each of a series of dilutions of this emulsion. After two weeks' incubation the highest dilution (smallest inoculum) showing true putrefaction gives an approximate but very definite quantitative estimation of the number of putrefactive organisms present per gram of stool.

By this simple, direct method the success or failure of any therapeutic measure in reducing the numbers of putrefactive organisms in the intestinal tract or in eliminating them completely may be determined by subsequent stool examinations at appropriate intervals during treatment, and the permanence of the result may be checked by repeating the examination at intervals thereafter.

TECHNIC

Preparation of media. All visible fat is removed from fresh beef which is then ground up finely in a meat grinder, and an equal weight, or more, of water added. Heat very gently with occasional stirring until the meat darkens slightly, then heat rapidly to the boiling point and remove. Titrate to neutrality (brom-thymol blue). Allow to stand over night in the ice-box. Skim off the fat. Fill test-tubes about one-third full and autoclave for one hour under 15 pounds pressure at 120°C.

Preparation of stool emulsion. In order to obviate the necessity of weighing out a definite quantity of each stool sample, a unit of convenient size was selected as that amount of stool which would fill an ordinary medium-sized bone curette. A large number of different stool units obtained in this manner were accurately weighed and the results averaged. The average weight was found to be approximately 0.2 gram. The spoon of the curette is filled tightly by pressure against the side of the container, the excess about the edges is wiped off and the unit then transferred to 10 cc. of physiological saline solution.

When thoroughly emulsified, 1 cc. of this emulsion is transferred to 9 cc. of physiological saline solution by means of a 1 cc. pipette and mixed. One cubic centimeter of this dilution is transferred to another tube containing 9 cc. of physiological saline solution, and so

on for the complete series of dilutions. The approximate dilution of the stool in the first tube (0.2 gram in 10 cc.) is 1 to 50; in the second, 1 to 500; in the third, 1 to 5000 and so on to the sixth tube, in which the dilution is 1 to 5,000,000. Any convenient size of stool unit may be used, it being only necessary to know the approximate weight. Nine dilutions were made as a routine in the work reported below, but putrefaction never occurred beyond the sixth dilution.

Inoculation of meat tubes. The sterile meat tubes to be inoculated are placed in a boiling water bath for at least 15 minutes to expel the air, and should be agitated occasionally to dislodge bubbles. They are then plunged into cold water and, when cool, should be used immediately.

One cubic centimeter of each dilution of the emulsion, previously prepared, is then introduced into a meat tube, a separate sterile pipette being used for each operation. Each meat tube is then sealed by pouring in a layer of melted petrolatum about 1 to 2 cm. thick and the cotton stopper replaced.

Incubation and examination of meat tubes. The inoculated meat tubes are incubated for two weeks at 37°C. and then examined for evidences of putrefaction. While this delay is inconvenient, it is necessary, because this length of time is sometimes required for the appearance of definite putrefaction when only a small number of putrefactive organisms are present.

Gas always appears in some of the tubes within 48 hours, pushing up the petrolatum plug, and is always found in the tubes representing very high dilutions of the stool at the end of 2 weeks. While some of this gas is formed in the process of true putrefaction, most of it results from the activity of saccharolytic anaërobes such as *Clostridium welchii* as well as organisms of the colon-aërogenes group which may grow under these anaërobic conditions, and which are present in much greater numbers than putrefactive organisms.

True putrefaction is unmistakable. The plug is pushed up by the gas formed. At least part of the meat has become liquefied. The particles remaining have become dark in color and even black in spots. Their edges have taken on a fuzzy appearance and all stages of disintegration may be seen. The peculiarly disagreeable odor of true putrefaction is present and snow-white spots of tyrosin crystals may be visible here and there throughout the media.

Ordinarily, the tubes representing dilutions far beyond those in which true putrefaction may be visible, show evidences of the activity of saccharolytic organisms. In these tubes large amounts of gas are formed, sometimes blowing the petrolatum plug and cotton stopper out of the tube. The meat is not reduced in volume and assumes a bright red color.

Interpretation. Since the amount of stool present in each dilution is known, the maximum and minimum number of putrefactive organisms per gram of stool may be figured from the highest dilution showing putrefaction. For instance, if only the first meat tube, which contains 0.02 gm. of stool, shows putrefaction, we may conclude that there are at least 50 putrefactive organisms present per gram of stool, and since the second meat tube containing 0.002 gm. of stool shows no putrefaction, we may likewise conclude that there are less than 500 putrefactive organisms per gram of stool. The actual number lies somewhere between these two figures.

All of the stools examined in this study showed a large preponderance of saccharolytic anaërobes over the putrefactive varieties. To check the possibility of an inhibitive action on the putrefactive types by the more numerous saccharolytic organisms present, meat tubes were inoculated with pure cultures of each type in various proportions. It was found that putrefaction of the meat proceeded regularly when inoculated with small numbers of putrefactive organisms in the presence of an overwhelming number of saccharolytic anaërobes. The stock cultures used were originally prepared by the single cell method.

INCIDENCE AND DEGREE OF INTESTINAL PUTREFACTION IN MAN

In the course of these and previous studies on intestinal putrefaction, 575 fresh stool specimens from 127 subjects, not under treatment with di-hydranol, were examined for the presence of putrefactive anaërobes by the method described above. Of this number 181 stools (31%) showed no putrefaction whatever, while 256 stools (45%) showed none beyond the first dilution. In other words, three-quarters of the stools showed only slight putrefactive properties or none at all.

Of the 138 stools remaining, 106 specimens produced no putrefaction

beyond the second dilution (73 stools) or third dilution (33 stools). That is, only 18% of these specimens showed even moderate putrefactive properties.

Thirty-two stool specimens produced putrefaction in the fourth (24), fifth (5) or sixth (3) dilution. In other words, less than 6% of the 575 samples showed what might be regarded, on this basis, as pronounced putrefactive properties.

In summary, if 4 or 5 stool specimens from each of a large group of subjects under no dietary control are examined for putrefactive properties by the method described above, about three out of four will show only feeble putrefaction or none at all; about one out of five will show moderate putrefaction, and only about one out of twenty will show pronounced putrefactive properties.

If the results of the examination of these 575 stool specimens are examined from the standpoint of their distribution among the 127 subjects furnishing them, we find the following:

1. In addition to the 21 subjects whose stools never produced any putrefaction whatever, the stools of 39 subjects never showed putrefaction beyond the first dilution. In other words, the stools of about half of these 127 subjects never showed any thing more than *slight* putrefactive properties.

2. One or more of the stools of 42 subjects produced putrefaction only in the second (26) or third (16) dilution as a maximum, which is to say—the stools of only about one out of three subjects showed even *moderate* putrefactive properties.

3. The stools of 25 subjects produced putrefaction in the fourth (17), fifth (5) or sixth (3) dilutions as a maximum at one time or another; that is, only about one out of five subjects ever produced a stool showing *pronounced* putrefactive properties.

The stools of 28 subjects (22%) showed at least slight putrefactive properties at every examination, while those of 21 subjects (17%) never showed any at all.

Although these generalizations might require some revision in a more comprehensive statistical summary, the number of specimens examined and the number of subjects furnishing them are sufficient to support the conclusion that intestinal putrefaction in man is by no means the constant and universal process it has been generally supposed to be.

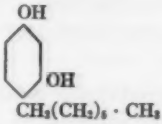
The examination of at least three or four stool specimens is necessary to classify a patient in one of these three arbitrary groups because of the variability in the putrefactive properties of the stool samples obtained at short intervals or on successive days. It is this individual variation in the same subject from day to day which accounts for the difference in the pictures presented when these results are examined from the standpoint of a classification of the 575 stool specimens and then from the standpoint of their distribution among the 127 subjects furnishing them.

None of the 127 subjects in these and in subsequent experiments were under any dietary control whatever. The variations shown may have been due in part to controllable factors such as the amount of protein ingested, especially meat, or to the actual ingestion of significant members of putrefactive organisms in certain foods.

It is possible that certain clinical groups will be found to be characterized by a rich and constant putrefactive flora in the stools. While this is uncommon in apparently normal adults, it does, nevertheless, occur, and may be easily proved by direct examination. Furthermore, the putrefactive flora may be reduced to insignificant numbers or eliminated completely by oral administration of di-hydranol. It would appear, therefore, that conjecture and guesswork as to the possible clinical importance of intestinal putrefaction is no longer necessary. The answer may be found in suitably controlled bacteriological examination.

DI-HYDRANOL

Di-hydranol (2-4-dihydroxyphenyl n-heptane) is a white crystalline substance of the following structure:



This synthetic complex is one of an extensive homologous series prepared for the writers' studies on antiseptics by the Chemical Research Department of Sharp and Dohme. Chemically, it may be

regarded as a heptyl derivative of resorcinol or as a hydroxyphenyl derivative of heptane.

Di-hydranol is only very sparingly soluble in water but is freely soluble in alcohol, ether, chloroform, glycerine, vegetable oils and alkalis. It is a stable compound, withstanding distillation under diminished pressure without decomposition.

Activity. Like other members of this series, di-hydranol is characterized by extremely powerful bactericidal activity in conjunction with very low toxicity. At body temperature it yields a phenol coefficient of about 130 by the U. S. Hygienic Laboratory method. It shows a definite selective activity in the higher dilutions against Gram-positive organisms (8) and is very strongly protozoacidal (9).

Toxicity. Di-hydranol, dissolved in vegetable oils (olive oil or cotton seed oil) has been fed to 12 rabbits by stomach tube in single doses of 1 gm. to 2.5 gms., and has been administered to 4 rabbits, in the same manner, in daily doses of 0.5 gm. (0.166 gm. to 0.2 gm. per kilogram of body-weight) for 10 consecutive days without discernible toxic effect. Autopsies on the animals receiving large single doses, and on two of the animals at the conclusion of this course revealed no pathological change on gross examination, and all the important parenchymatous organs appeared to be normal on microscopic examination. The animals saved for observation over a period of 4 months gained weight and remained normal in all respects. Daily examination showed the urine to be normal during the course, and the functional capacity of the kidneys, as determined by phenolsulphonphthalein, remained normal in each case throughout the period of observation.

Ratcliffe (9) has fed 10 rats on a stock diet in which 1 per cent of di-hydranol had been incorporated. Each rat received 10 gms. of this diet for 15 consecutive days (1.5 gm. di-hydranol) without toxic effect.

Ketron (10) has administered elastic gelatin capsules each containing 0.15 gm. di-hydranol in 25% solution in olive oil to a group of 42 adult men and women, in doses of 0.45 gm. three times daily after meals, for periods varying from one to five weeks. In previous experiments, and in those to be reported in detail below, the writers have administered this product in doses of 0.3 gm. to 0.6 gm. (2 to 4

capsules) three times daily after meals to 37 normal men for periods varying from one to six consecutive weeks. Aside from slight transitory gastric irritation, which occurred occasionally and an occasional diarrhea or constipation lasting one to two days when first starting treatment, no toxic result has been observed in these two groups.

Faust (11) has administered di-hydranol to dogs and to monkeys by duodenal tube; to rats, by incorporating one per cent of the drug in a balanced diet, and to eight children, from 2 to 9 years of age, in the form of a 5 per cent solution in olive oil. The children received one teaspoonful (0.2 gm.) three times daily after meals for a week or more. Each host received 2 to 10 gms. di-hydranol. On the whole, he found the drug to be well tolerated. Slight gastric pain was noted in two children to whom the solution had been administered before meals, and in 2 out of 13 adolescents and adults receiving two capsules (0.3 gm.) after meals slight diarrhea developed for two days.

The writers subscribe to Faust's conclusion that the toxicity of di-hydranol is "clinically negligible."

Excretion. The bulk of each dose of di-hydranol taken by mouth passes through the alimentary canal unabsorbed. The drug may be detected by Barbour's test (12) in the urine of animals, one to three hours after a massive dose, but on ordinary clinical doses of 0.3 or 0.45 gm. three times daily, the urine of normal men shows only an occasional positive test. On the other hand, if a small portion of the stool of a subject receiving average doses is rubbed up with ether, filtered, and the ethereal extract evaporated to dryness and then taken up with a little dilute alkali, this solution invariably gives a strong test for the drug. It was this observation, first made by Dr. Herbert L. Ratcliffe, which suggested the present investigation of di-hydranol as an intestinal antiseptic.

In summary, di-hydranol is a stable non-toxic substance and a powerful germicide, with a selective bactericidal activity against Gram-positive organisms. It is administrable by mouth and remains largely unabsorbed in its passage through the alimentary canal.

CONTROL OF INTESTINAL PUTREFACTION IN MAN BY ORAL ADMINISTRATION OF DI-HYDRANOL

In order to test the activity of di-hydranol in reducing intestinal putrefaction in man, a group of 28 volunteers was selected. All were normal men, attached to the laboratory as staff members, students, or technicians, and therefore readily available for medication at stated hours and the collection of fresh stool samples.

Throughout these experiments, elastic gelatine capsules, each containing 0.15 gm. di-hydranol in 25% solution in olive oil, were employed.

Each subject reported to the laboratory daily at nine, twelve, and four o'clock, when the capsules were swallowed. When given at times other than immediately after meals, a glass of milk was provided. From Saturday noon to Monday morning each subject carried his own supply of capsules and was instructed to take three doses daily, after meals.

The observations were started with a group of 6 subjects. After the collection of two control stool samples, medication was started on September 21, with 2 capsules (0.3 gm.) t.i.d. This dose was increased on September 25 to 3 capsules (0.45 gm.) t.i.d. and continued without interruption until October 14 (19 days). On this date, treatment of a group of 22 new subjects, from each of whom 4 control stool samples had been obtained, was started with 2 capsules t.i.d. From October 14 to November 11 (29 days), when all medication was discontinued, all 28 subjects received 2 capsules t.i.d.

Fresh stool samples were secured three times each week from each subject throughout the course, and for three weeks after stopping medication. Two months and again four months after stopping medication one or more stool samples were obtained from each subject. All stool samples were examined for putrefactive properties in Holman's cooked meat media by the method described above.

Nearly eight hundred stool examinations were made on this group of 28 subjects during the period of observation, each stool being examined in nine dilutions. The tabulation of this mass of material is too bulky for reproduction, but in its analysis, a few facts stand out very strikingly:

1. The stools of 2 of these 28 subjects never produced any putrefaction whatever, before, during, or after treatment.

2. One or more of the control samples of stools obtained from each of the remaining 26 subjects before treatment showed putrefactive properties. Six subjects furnished stools, before treatment, showing putrefaction only in the first dilution; seven, in the second dilution; five, in the third dilution; four, in the fourth dilution, and two each in the fifth and sixth dilutions. In other words, according to the arbitrary classification given above and intended to express roughly the degree of intestinal putrefaction, these 26 subjects would be grouped as follows: slight, 6; moderate, 12; pronounced, 8. This is a greater incidence of intestinal putrefaction than was found in the analysis of the 127 subjects previously described as a group.

3. In 12 of the 26 subjects, no stool was ever obtained after the first 48 hours of treatment with di-hydranol, which produced putrefaction even in the first dilution. Had treatment not been continued, putrefactive properties may have reappeared. However this may be, the stools of these 12 subjects remained permanently negative.

4. In 7 of the remaining 14 subjects no stool was ever obtained after the first 48 hours of treatment which produced putrefaction beyond the first dilution. The stools of these 7 subjects became permanently negative on the 3rd, 4th, 6th, 7th, 11th, 14th and 35th days, respectively. The last named subject represented a particularly stubborn case. His control stools showed putrefaction out to the fourth dilution, dropped rapidly to the second and then to the first dilution in less than a week, but did not become permanently negative for nearly one month thereafter.

5. The control stools of one of the remaining 7 subjects showed putrefaction in the third dilution. From the 8th to the 36th day of treatment the 12 stools examined were all negative. Then putrefaction appeared in one sample in the sixth dilution. The stools then became permanently negative.

In another similar case, the control stools showed putrefaction in the third dilution, became negative within 48 hours after treatment was started, remained negative until the 25th day, and then suddenly showed putrefaction in the second dilution. The stools of this subject then became permanently negative. In a third case of this type,

putrefaction appeared in the second dilution of the stool obtained on the 17th day. The stools had been negative before this, with one exception, since the 3rd day of treatment. They became permanently negative after the 17th day.

6. One of the 4 subjects remaining showed moderate but very constant putrefaction. The stools became permanently negative on the 18th day. The other 3 subjects all showed pronounced putrefaction out to the sixth dilution, and proved to be unusually resistant to treatment. In two of these subjects putrefaction never occurred beyond the second dilution after the first week's treatment, but nearly every stool showed some putrefactive properties up to the 27th day in one case, and up to the 41st day in the other, when the stools became permanently negative.

In the third stubborn case, the stools showed pronounced and constant putrefactive properties and appeared to be unaffected by treatment until the 18th day. On this day the stool sample showed violent putrefaction in the sixth dilution. There then occurred a complete and permanent disappearance of putrefactive properties in the stools of this subject. Of the 14 stools subsequently examined over a period of four months, none produced any putrefaction whatever.

7. All medication was discontinued on November 11, 6 subjects having been under treatment for 52 consecutive days, and 22 subjects for 29 consecutive days. The stools of 2 subjects did not become permanently negative until the 35th and 41st days, respectively. These two subjects were in the first group. Otherwise, treatment would have been insufficient. All 28 subjects had furnished several consecutive negative stool samples before treatment was discontinued on November 11.

8. Examination of three stools weekly from each subject for three weeks following discontinuance of treatment failed to show any putrefaction whatever in any case.

9. In the middle of January, two months after treatment had been discontinued, one or more stool samples were examined from each of these subjects. None of these stools showed any putrefactive properties.

10. In the middle of March, four months after treatment had been

discontinued, a single stool sample from each subject proved to be devoid of putrefactive properties in every case.

Discussion. It should be explained, perhaps, that in using the expression "permanently negative" in connection with the absence of putrefactive properties, the writers intend to limit the meaning of the words merely to the period of their observations. The relative permanence of the result, *i.e.*, the failure of even slight putrefactive properties to reappear in any case within four months after treatment was even a greater surprise than the astonishing fact that organisms capable of causing true putrefaction were apparently eliminated completely from the intestinal flora of every one of the 26 subjects who undoubtedly harbored them before treatment.

The clinical significance of the results described in this paper depends upon the actual importance of true intestinal putrefaction, as a direct or contributing factor in the etiology of functional or organic disease. The writers assume no position at present on this highly controversial question. Three facts clearly pointed out in this paper, however, demand emphasis:

1. Intestinal putrefaction is usually a mild and irregular phenomenon, although instances in which it may be a constant and fairly active process are by no means uncommon.

2. Since the organisms of true putrefaction are spore-bearers, the putrefactive properties of the stools may be taken as a measure of intestinal putrefaction. The presence or absence of intestinal putrefaction in a given case as well as its intensity may therefore be proved by simple, direct, bacteriological methods.

3. The administration of di-hydranol (2-4-dihydroxyphenyl n-heptane) in doses of 0.3 gm. to 0.45 gm., three times daily, destroys the true putrefactive flora of the intestinal tract with great certainty and regularity.

REFERENCES

(1) *Proc. Royal Society of Medicine*, 1913, vol. 6, part 1, p. 1.
(2) ALVAREZ, WALTER C.: *Physiological Reviews*, 1924, vol. 4, p. 352.
(3) SCHIEBLICH, MARTIN: *Zntralbl. f. Bakteriol.*, (Abt. 1), 1929, Bd. 112, p. 188; p. 206; p. 497; p. 505. *Ibid.*, 1929, vol. 113, p. 41; p. 55.
(4) BERGHEIM, OLAF: *Jour. of Biol. Chemistry*, 1924, vol. 4, p. 352.
(5) *Idem: Ibid.*, 1924, vol. 62, p. 45.

(6) Editorial: *Jour. Amer. Med. Assn.*, 1925, vol. 84 (Jan. 17), p. 206.
(7) HOLMAN, W. L.: *Jour. Bact.*, 1919, vol. 4, p. 149.
(8) HAMPIL, B.: *Jour. of Infectious Diseases*, Vol. 43, No. 1, July 1928, p. 25.
(9) RATCLIFFE, HERBERT L.: *American Jour. of Hygiene*, Vol. 10, No. 3, Nov. 1919, p. 643.
(10) Personal communication.
(11) FAUST, ERNEST CARROLL: *Proc. of Society for Exp. Biology and Medicine*, May 24, 1930. *To be published.*
(12) BARBOUR, H. G.: *Canadian Medical Assoc. Jour.*, Vol. 15, August 1925, p. 787.

CARCINOMA OF THE STOMACH IN A SEVENTEEN-YEAR-OLD GIRL

ALEXANDER MARBLE, M.D.

From the Department of Medicine of the Johns Hopkins University School of Medicine

Because of the extreme rarity of carcinoma of the stomach in the first two decades of life, the case reported below is thought worthy of record.

CASE REPORT

Miss F. P. (J. H. H., No. 17738), a 17-year-old Italian school girl, was admitted to the Johns Hopkins Hospital on April 6, 1928, with the complaint of "weakness and pains in the stomach." Her family history was irrelevant. Her past history showed that she had lived in southern Italy until about 7 years before; she had enjoyed good health until her present illness. Childhood illnesses had been insignificant and were poorly remembered. A review of body systems revealed nothing remarkable.

Her present illness dated from May, 1927, 11 months before admission, at which time she began noticing generalized weakness which increased as time went on. She found that exertion produced shortness of breath, dizziness, and severe frontal headaches. It became evident to those about her that she was pale. By June or July, 1927, there had developed slight swelling of the ankles and puffiness about the eyes, more noticeable in the later part of the day. At about the same time there began epigastric pain, coming on fairly regularly about 30 minutes after meals and lasting 30 minutes. More food sometimes relieved, sometimes aggravated, the pain. After eating she often was nauseated and vomited. She frequently vomited at night time, gaining relief from pain thereby. The vomitus did not taste sour; there was never any gross, fresh blood, although the vomitus was often dark-colored. No abnormalities were noted in the stools.

This state of affairs prevailed until December 7, 1927, when she was seen in the Johns Hopkins Hospital Dispensary. At this time the striking features of the physical examination were pallor of the mucous membranes, moderately enlarged tonsils, many striae in the skin over the shoulders and hips, and some indefinite abdominal tenderness. The urine was reported as normal except for the presence of a small amount of sugar. The erythrocytes numbered 3,790,000 per cu. mm. and the hemoglobin was 34 to 49 per cent (Sahli). She was advised to enter the hospital, but refused to do so and was not heard from until April 2, 1928, when she

returned to the Dispensary. Surprisingly enough, her condition did not seem worse than it had been in December. Subjectively, she was in some ways better. This time she was persuaded to enter the Hospital and did so on April 6, 1928. She thought that her weight loss during the 11 months of illness was about 27 pounds.

Physical examination on the ward showed a thin, pale, Italian girl who appeared to have lost a good deal of weight. The actual weight was 107 pounds (without clothing). There was moderate tachycardia (pulse rate 100), no real fever, and a normal blood pressure (114/70). Other than moderately enlarged tonsils and the signs of loss of weight, the positive physical findings were those concerning a small, hard mass high in the epigastrium. It was at times tender, at other times, not. The readiness with which one could palpate the mass varied from day to day; it seemed sometimes directly in the midline and then at times to the right or left. However, it was a very definite mass which was felt distinctly by all on the staff who saw her. Rectal examination showed nothing abnormal.

Laboratory data showed an erythrocyte count of 3,940,000 per cu. mm.; hemoglobin 42 per cent, and leucocytes 6,960 per cu. mm. The blood smears showed marked central achromia and slight variation in size and shape of the erythrocytes; only rare reticulated cells were seen. The platelets were abundant. The urine was found always to be normal. The stools and gastric contents both gave strongly positive chemical reactions for blood. Titration showed the gastric contents after a test meal to contain 22 cc. of free HCl and 62 cc. of total acid per 100 cc. The Wassermann test was negative. Roentgenograms (barium series) of the gastro-intestinal tract showed a large defect in the pyloric end of the stomach. Fluoroscopic examination showed both greater and lesser curvatures to be very irregular in the lower third of the stomach, but without obstruction. Pressure over this area revealed a mass thought to be either on the posterior wall of the stomach or behind it. This mass was thought to be suggestive of a neoplasm. The duodenal cap was normal.

She was kept on the medical service 9 days for study. During this time she was practically afebrile (temperature below 99.6°) but ran a quite irregular pulse rate (88 to 140). On an ordinary Sippy diet without alkaline powders she did well, did not vomit, and had only one slight attack of epigastric pain. She was transferred to the surgical service on April 15th with the exact diagnosis in doubt. On the next day Dr. Dean Lewis did an exploratory laparotomy and found a large ulceration in the pyloric region along the lesser curvature of the stomach extending fairly well up toward the cardia. A subtotal resection of the stomach was done, removing the greater portion of the organ including the ulcerated area. The ends of the duodenum and the gastric remnant were closed separately and an anterior gastroenterostomy and an enteroenterostomy done. One of the regional lymph nodes was removed.

PATHOLOGICAL REPORT

(Surg. Path. No. 43253)

The surgical specimens were examined by Dr. Samuel S. Blackman. His report follows:

Gross description of material

The specimen is a rectangular-shaped portion of a stomach resected from the pyloric end. It measures 16 x 11 cm. On the inner surface along the lesser cur-

FIG. 1. PHOTOGRAPH OF THE RESECTED PORTION OF THE STOMACH SHOWING THE TUMOR MASS WITH THE LARGE CENTRAL ULCERATED AREA

vature there is a rounded, crater-like ulceration, 8 cm. in diameter. It is surrounded by a thick ridge which projects in places for a distance of 17 mm. The lateral surface of this ridge, and its crest in places, are covered by mucosa which looks normal grossly. On the inner surface of the ridge and on the floor of the ulceration there is a delicate, yellowish, fibrinous membrane. On section, there is a thick layer of soft, bluish-white, somewhat translucent tissue forming the base of the ulceration. In long branching strands and in thicker bundles it extends widely through both layers of the muscularis and into the serosa. The ridge forming the rim of the crater-like ulceration is composed of similar tissue. Laterally, it extends

for a short distance into the submucosa. There is a small lymph node, a millimeter in diameter, in a bit of omentum attached along the greater curvature of the stomach. On the cut surface of this node one sees here and there small patches of bluish-white tissue like that seen in the wall of the stomach.

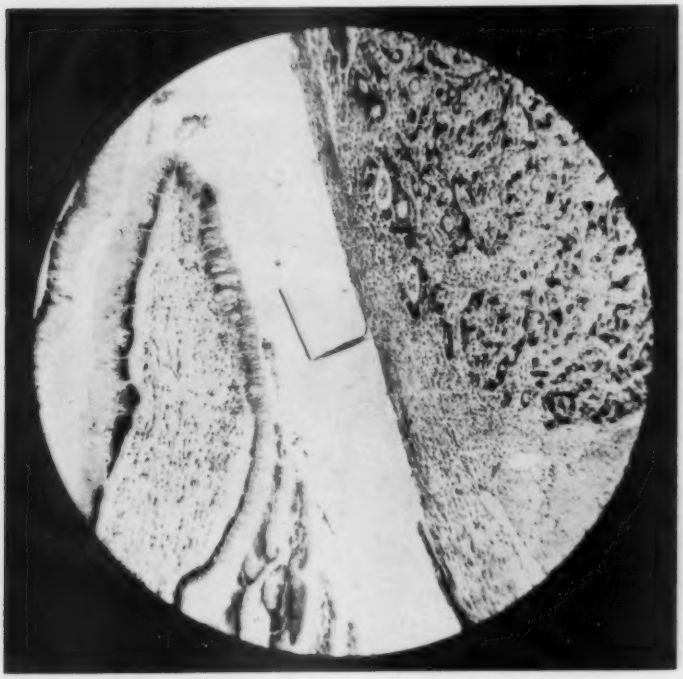


FIG. 2. LOW-POWER MICROPHOTOGRAPH OF A SECTION THROUGH THE STOMACH WALL SHOWING THE ALTERED GASTRIC GLANDS AND THE INFILTRATION OF THE MUSCULARIS BY SHORT CORDS OF TUMOR CELLS

Microscopic description

On the surface of the ulceration there is a fibrino-purulent exudate. The bluish-white tissue, which forms the base of the ulceration, infiltrating the muscularis and serosa below, and which forms the ridge-like margin, extending into the submucosa beyond, is composed of a rather loosely arranged fibrous connective tissue, infiltrated with epithelial tumor cells. These epithelial cells are distributed rather uniformly in small numbers throughout the relatively abundant fibrous

stroma. For the most part they are distributed as single cells, but sometimes in small groups, and rarely they form short strands with a distinct acinar and tubular arrangement. The mucosa over the external surface and crest of the ridge surrounding the excavation contains glands which are distinctly abnormal. Some are very long, tortuous, and wide. It is possible to trace a transition from such modified epithelium to distinct tumor cells which are infiltrating the wall of the stomach. These cells extend in places over the surface of the ulceration in single

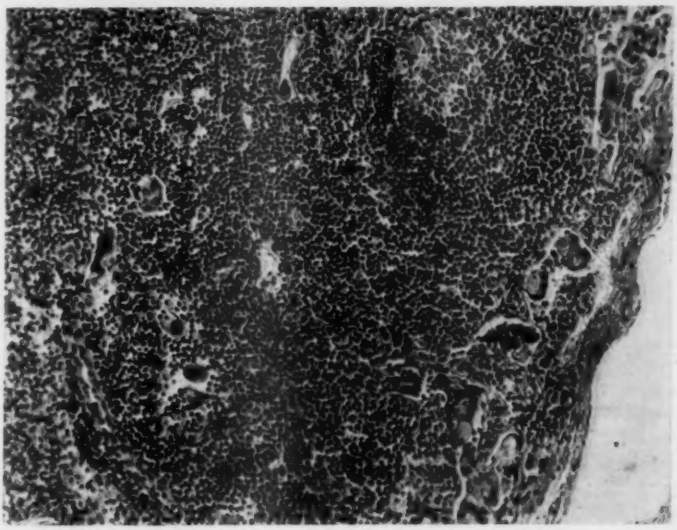


FIG. 3. HIGH-POWER MICROPHOTOGRAPH OF A SECTION THROUGH A REGIONAL LYMPH NODE

Note the tumor cells in the lymph sinuses

layers of columnar epithelium. The tumor cells are quite variable in size and shape. Many contain large, irregular, deeply stained nuclei. Mitotic figures are frequently seen.

There are metastases in the lymph node. The peripheral lymph sinuses contain tumor cells occurring singly and in small clumps. Some of these clumps have a distinct alveolar and tubular arrangement. Section through the middle of the node shows that much of it is replaced by tumor tissue. As in the stomach, the fibrous stroma is very abundant and contains relatively small numbers of scattered tumor cells.

Impression. Adeno-carcinoma of the stomach with metastases in a regional lymph node.

POST-OPERATIVE COURSE

The post-operative course was essentially uneventful. On the 27th of April (11th day post-operative) her erythrocyte count was 3,700,000 and hemoglobin 37 per cent. On the next day, she was transfused with 500 cc. of whole blood. Again on the 20th of May, she was transfused with 600 cc. of whole blood, using her father as donor. She was discharged on May 25th with an erythrocyte count of 4,480,000 and hemoglobin of 92 per cent. Tests for occult blood in the stools were negative. Her weight on discharge was 109 pounds (without clothing). She reported on June 7th with a story of chills and fever since discharge. Blood smears showed malarial parasites, and she was again admitted on June 29th. Quinine sulphate was administered with immediate improvement and at the time of discharge on July 26th, she had been afebrile for some days. She was asymptomatic except for occasional vague abdominal discomfort. The presumption was that the malaria was contracted through the blood obtained from her father at the last transfusion particularly since the father was found to have a palpable spleen. The father disclaimed ever having had malaria, however, and no parasites were found in smears of his blood. A few days before discharge, the patient's erythrocyte count was 4,100,000 and her hemoglobin 92 per cent. Stools were negative for occult blood. X-ray showed "resection at pyloric end of stomach; stomach is completely empty at end of five hours; no lesion can be made out."

SUBSEQUENT COURSE

On June 15, 1929, 14 months after her operation, she reported by request to the Dispensary. She considered herself well and had no complaints except occasional generalized aches in the lower back after exercise and puffiness about the ankles at the end of a day on her feet. She had been normally active and had been eating an unselected diet without discomfort, epigastric fullness, or pain. She had had no vomiting, no dizzy spells, no headaches, no fever, and no exertional dyspnoea. Examination showed her to be looking well. Her weight (with clothing) was 134½ pounds. There was no jaundice. The heart showed no murmurs. Her operative scar was well healed; there was no abdominal tenderness and no masses could be felt. The liver, spleen, and kidneys could not be palpated. There was some puffiness but no pitting edema of the ankles. The blood pressure was 124/70. The erythrocyte count was 4,350,000 and hemoglobin 72 per cent (Sahli). Accordingly, except for persistent slight secondary anaemia, there was no suggestion of a remaining carcinomatous process.

On September 27, 1929, she was readmitted to the Johns Hopkins Hospital complaining of pain in the epigastrium and in the right lower quadrant of the abdomen, difficulty in the passage of solid food from the mouth to the stomach, loss of weight and easy fatiguability. She was found now to have an enlarged liver and a large firm mass in the upper mid-abdomen. Roentgenograms of the gastro-intestinal tract and of the bones showed no evidence of carcinoma; despite this, it was felt that without doubt the epigastric mass represented a recurrence of the malignant

process. The family were so informed and the patient was discharged on October 1, 1929.

On November 6, 1929 she was seen at the West Baltimore General Hospital. A note concerning this visit was made on her Johns Hopkins Hospital record by Dr. Harold E. Wright as follows:—"X-ray examination showed extensive resection of the whole prepyloric end of the stomach. Scarcely anything remains in the stomach, but [the barium] passes directly through and into the jejunum. The patient is vomiting a great deal and is very anxious to have something done to prevent this vomiting."

Shortly after this, the patient came again to the Johns Hopkins Hospital and was referred to the Dr. Howard A. Kelly Hospital for radium treatment. She had one treatment but did not return. Her condition steadily became worse and she died at home on February 8, 1930. No autopsy was performed.

DISCUSSION

The outstanding features in this case are:

(a) *Age.* From time to time, isolated cases of gastric carcinoma in the young have been reported. In 1900 Osler and McCrae (1) in their monograph on "Cancer of the Stomach" collected from the literature 6 cases in the first and 13 cases in the second decade of life. They recognized that, particularly in the cases below the age of 10, the exact diagnosis is a matter of some doubt. Sullivan (2) in 1924 reported a case in a man of 22 years and reviewed the literature. Altogether, he mentions 25 cases occurring in the first 2½ decades of life and of these, 21 occurred in the first 20 years. In this number he did not include 13 of the cases (20 years of age and under) mentioned in the list compiled by Osler and McCrae. Accordingly, if one chose to accept without further question the entire group, one would find 34 reported cases in the first 2 decades of life up until the time of Sullivan's paper. Since then Kretzler (3), Barr and Allerton (4) and Mogena (5) have reported cases occurring in patients of 22 years, and Head (6) and Blagdon (7) have reported cases in patients of 24 and 25 years, respectively. Only three cases, those of Begtrup (8) in an 18-year-old man, of Stewart (9) in an 18-year-old patient, and of Wheeler (10) in a 20-year-old man, have been reported as occurring at the age of 20 or below. These, with the case described in the present paper, bring the total number of reported instances in the first 2 decades to 38. This list is probably incomplete, since an exhaustive review of the literature has not been attempted.

(b) *Sex.* In the 38 cases noted above, only 6, those of Moore (11) in a 13-year-old girl, of Schlesinger (12) in a 14 and a 17-year-old girl, of Ruetimeyer (13) in a 19-year-old girl, of Hirtz and Lesne (14) in a 19-year-old girl, and in the patient recorded in this paper, are reported as occurring in females This preponderance in males has been frequently commented upon in the literature. No explanation has been suggested.

(c) *Duration of the disease.* Carcinoma of the stomach in the young usually shows a somewhat sudden onset and runs a rapid course with death within a few weeks to a few months after the beginning of symptoms. However, one of Ruetimeyer's (13) cases (not the one referred to above) lived for about 3 years from the time of onset of gastric symptoms; this boy (aged 15) lived about 1½ years after gastroenterostomy and pyloric resection. In the case reported in this paper, the illness had lasted about a year before operation and death did not take place until about 22 months after operation. For at least the first year of this post-operative period she was almost symptom-free. As nearly as one can estimate, the total duration of her disease from the onset of symptoms was about 2 years and 9 months. Despite the eventual outcome, operation certainly afforded a long period of relief and was distinctly worthwhile.

(d) *Diagnosis.* Since such cases are so rare it is scarcely profitable to discuss at any length the matter of exact diagnosis. The experience with this patient emphasizes the fact that if the history, physical examination, or roentgenograms suggest the presence of carcinoma of the stomach, the question of age should not be accorded undue weight. Rather, exploratory laparotomy should be given proper consideration since, as in this case, subsequent months may be made much more comfortable and the period of useful life may be prolonged. The question of differential diagnosis between gastric sarcoma and gastric carcinoma has been adequately discussed by Sullivan (2) and need not be reviewed here.

SUMMARY

An unusual case of carcinoma of the stomach is reported. The patient was a girl seventeen years of age when first seen. The total duration of the disease from the onset of symptoms was about 33 months; the length of life after partial gastrectomy was 22 months.

The writer wishes to thank Dr. W. T. Longcope for permission to publish this case, Dr. S. S Blackman for the description of the surgical specimens, Dr. H. E. Wright for certain of the post-operative data, and Dr. G. A. Bennett for one of the microphotographs.

REFERENCES

(1) Osler, W., and T. McCrae: Cancer of the Stomach. Philadelphia, P. Blakiston's Son & Co., 1900.

(2) Sullivan, R. P.: Carcinoma of the Stomach in Young People. *Surg. Gynec. Obst.*, 1924, **39**, 283.

(3) Kretzler, H. H.: Carcinoma of the Stomach in a Man of Twenty-two Years. *Northwest Med.*, 1926, **25**, 146.

(4) Barr, C. C., and P. Allerton: Carcinoma of the Stomach in Young Adults. *Nebraska M. J.*, 1928, **13**, 103.

(5) Mogena, H. G.: El cáncer gástrico juvenil. *Arch. de med. cir. y. espec.*, 1927, **26**, 580.

(6) Head, J. R.: Cancer of the Stomach in a Man Aged Twenty-four. Wisconsin M. J., 1926, **25**, 342.

(7) Blagdon, L.: A Case of Cancer of the Stomach in a Young Woman of Twenty-five Years. *Union méd. du Canada*, 1929, **58**, 415.

(8) Begtrup, E.: Et Tilfaelde af Cancer ventriculi hos en 18-aarig Mand. *Hospitalstid.*, 1925, **68**, 477.

(9) Stewart, M. J.: Discussion on Carcinoma of the Stomach in the Proceedings of the Section of Surgery at the Annual Meeting of the British Medical Association at Bath, 1925. IV. Pathology: General Relation of Carcinoma to Ulcer. *Brit. M. J.*, 1925, **2**, 882.

(10) Wheeler, W. I. D.: See (9) above. I. Diagnosis. *Brit. M. J.*, 1925, **2**, 875.

(11) Moore, N.: Carcinoma of Stomach in a Child. *Tr. Path. Soc. London*, 1884–5, **36**, 195.

(12) Schlesinger, H.: Unterscheidet sich das Magensarkom klinisch vom Karzinom? *Wien. klin. Wchnschr.*, 1916, **29**, 785.

(13) Ruetimeyer, L., Zum klinischen Verhalten des Magencarcinoms. II. Magencarcinom im jugendlichen Alter. *Corr.-Bl. f. schweiz. Aerzte*, 1900, **30**, 706.

(14) Hirtz, E., and E. Lesne: Epithélioma généralisé à toutes les parois de l'estomac chez une femme de dix-neuf ans. *Méd. mod.*, 1896, **7**, 481.

BOOK REVIEWS

Physician and Patient. Personal Care. Edited by L. Eugene Emerson. 8°. 244 pp. (*Harvard University Press, Cambridge, 1929.*)

One of the most encouraging tendencies of medical teaching is an effort not only to cultivate the personal relationship between doctor and patient but to dignify it in the eyes of the student. For purposes of teaching, the conception of the patient as a human being with the most subtle and sensitive reactions has been left to the psychiatrist, who has been saddled not only with the responsibility of developing his science but also with the task of injecting it into the professional mind. This is an office well within the province of medical teachers, who have too often been gifted in science or devoted to the humanities but neglectful of humanity itself. It is fitting that Harvard, with its prestige and its fine tradition of medical practice, should undertake the task of bringing such a concept to its students.

This volume contains a series of addresses on the Care of the Patient given by the distinguished physicians before the students of the Harvard Medical School and designed "to set the official seal of approval by the highest authority possible on the idea that the patient is a person, not a test-tube in a laboratory, or an aggregation of organs, or a mere machine . . . . ." The fine essay of the late Dr. Peabody, which was one of this series, has been printed separately and is not included in this volume.

Dean David Edsall's scholarly address on "The Human Relations of Doctor and Patient" is well chosen to open the volume and strikes the keynote. It is the essence of humanness and one wishes that it might fall under the eye of every student and doctor. "The Medical Education of Jones, by Smith," is a delightfully written sketch presented by Dr. William S. Thayer. It tells of the inspiring influence of Osler, who walks through the pages as Fowler (doubtless from l'Oiseleur), on the life of the young man Jones. The writing has a charm that makes the identity of both Smith and Jones easy to guess. The book also contains addresses by Dr. C. F. Martin, Austin Fox Riggs, Franklin G. Balch and Lawrence K. Lunt and ends with three by Alfred Worcester on "The Care of the Aged," "The Care of the Dying" and "Sex Hygiene," all of which are helpful and eminently readable.

Many will welcome this opportunity to have the addresses in permanent form. It is doubtless true, however, that most of the volumes will fall into the hands of those who already have a sincere interest in the care of the patient, but one hopes that some of these contributions may swing in a wider arc by republication in the journals. To our knowledge this has been done only in the case of Dr. Thayer's address which appeared in the Harvard Graduate Magazine.

D. McE.

Methods of Biological Assay. By J. H. Burn, M.A., M.D. (Camb.). With an Introduction by H. G. Dale, C.B.E., Sec.R.S., M.D., F.R.C.P. 126 pp. $2.25. (*Humphrey Milford, Oxford University Press, 1928.*)

This little volume is a welcome addition to the literature of pharmacology. The important methods employed in the biological assay of some of our important drugs are described clearly and concisely. The author states in the opening sentence to the preface that he has given descriptions of those methods only with which he has had personal experience. It is generally known that he has had a wide experience in this field, and for that reason the few criticisms here offered are not intended as a reflection on his experience, but for the purpose of calling attention to certain shortcomings in the present book, which, if rectified in subsequent editions, will add greatly to its usefulness, especially in this country. The treatment of the blood pressure test for the assay of posterior pituitary extracts is inadequate. Certain pertinent objections to the use of the decapitated cat for estimating the potency of posterior pituitary extracts are given, and yet no mention is made of the method in which the anesthetized dog or cat is used—a method very commonly employed in this country. Furthermore, now that the two separated fractions of the posterior lobe hormone (pitoxin and pitressin) have been accepted by the Council of Pharmacy and Chemistry of the American Medical Association, it is essential that both the oxytocic and pressor methods for the assay of posterior pituitary preparations receive proper attention, since both methods will have to be employed. The oxytocic method does receive adequate treatment. The only method for the standardization of epinephrine (adrenalin) given is the blood pressure of a spinal cat. No reference is made to the use of an anesthetized dog which is the official method given in the United States Pharmacopeia. In the chapter dealing with the assay of antipyretic drugs, it would be well to give other pyretic substances in addition to the heated cultures of *B. coli*, such as peptones, cocaine and β-tetrahydronaphthylamine.

It would be desirable to have a more inclusive list of references. For example, at the end of the chapter on digitalis assay a reference to Hatcher and Brody's original paper might be given. Similar omissions have been noted in other parts of the text. The introductory chapter, written by Dale, in which the general principles in this type of work are emphasized, is well done and very useful.

E. M. K. G.

Handbook of Bacteriology for Nurses. By Harry W. Carey, A. B., M.D. 3rd revised and enlarged ed. Illustrated. 282 pp. $2.25. (*F. A. Davis Company, Philadelphia, 1930.*)

In reviewing a textbook of bacteriology for nurses it is necessary to keep in mind the fact that the subject is being presented to a group of women who, for the most part, have had little or no scientific training. This is a difficult task which Dr. Carey, on the whole, has executed adequately. However, considering these facts, we feel that the author might well have devoted more attention to the introductory

chapters which he hurries through in a manner which leaves even one with some acquaintance with the subject a trifle breathless.

In the presentation of the material the author has been very successful. He gives clearly and concisely the fundamental facts of bacteriology in a few hundred pages. He includes in the textbook a great deal of material, which he handles in a very simple yet satisfactory manner, and consistently correlates his subject matter with the use a nurse may find for such knowledge.

The arrangement of the section of the book dealing with the various pathogenic bacteria, however, is very unsatisfactory. For example, in a series of chapters headed "Bacteria Causing Acute Infections" he discusses, side by side, diphtheria, cholera, tularemia, anthrax and the diseases caused by organisms having no relation to one another, without making any attempt at classification—an arrangement which could not help but be confusing to the beginner. There are also mistakes which should not appear in the third edition of a textbook; for example, errors in the classification of Gram-positive and Gram-negative rods.

The illustrations are quite good and the review questions at the end of each chapter helpful. The laboratory exercises suffer, however, from the same lack of clear and definite arrangement and classification as does the text itself. The exercises are in themselves adequate, but the lack of any clear plan of study detracts from their usefulness. If the really excellent material were arranged according to some definite outline which would be less confusing to the student nurse, and the small errors were corrected, this would be a very commendable text-book for the purpose for which it is intended.

I. G.

Insects, Ticks, Mites and Venomous Animals of Medical and Veterinary Importance. Part 1. Medical. By W. S. PATTON, Professor of Entomology, and A. M. EVANS, Lecturer on Entomology, Liverpool School of Tropical Medicine. Pages x + 786. Plates LX. Figures 374. 1929. (Obtainable only from the *Entomological Department, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, England.*) Price, 20 shillings (with duty, about $5.00).

This book is intended to replace Patton and Cragg's "Textbook of Medical Entomology," which is out of print. It contains a wealth of information on the morphology, life histories and bionomics of all arthropods of importance in human medicine.

In its presentation of the subject, the book frankly conforms to the course for the Diploma in Tropical Medicine, as given at the Liverpool School. There is no Table of Contents, no list of plates or figures, and no bibliography. Instead of being divided into chapters, it is arranged in 28 "meetings" of the class. Under each of these there is given a synopsis of the lecture, followed by descriptions, illustrations and discussions of each of the demonstration specimens examined by the students during the laboratory period. This form, although doubtless very convenient for the particular course illustrated, makes it a little difficult to use

the book as a reference work. This difficulty, however, is somewhat relieved by the presence of a comprehensive index.

In this book, the emphasis is placed on structure, early stages and relation to human disease, with comparatively little space devoted to classification and identification. It seems rather too bad, by the way, to include in this "Part" the beautiful figures of 18 species of *Anopheles*, by Terzi, when the text only remarks (page 262) that "the classification of the Anophelini and the identification of the species of *Anopheles* will be dealt with in Part 3."

The very numerous illustrations, from drawings by Mrs. Patton, Miss Evans and Mr. Terzi and photographs by Miss Brown, are uniformly excellent, and would of themselves make the book indispensable to every medical entomologist, even without the valuable descriptions of and comments upon them contained in the text. Major Patton's extensive field and laboratory experience in the Orient enables him to speak with authority on the insects and diseases of the Old World Tropics. When he deals with diseases which have been studied mainly in America, he is not always equally accurate. It is surprising to find on page 297, for example, the following statement: "Tularaemia. This disease, which is caused by a filter-passing virus, gets its name from Tulare, a town in the State of Utah, U. S. America, where it is common."

On the whole, however, this work must be considered a real contribution to science, and one which will be of very great value to workers on arthropods in relation to human diseases.

F. M. R.

Nursing Mental Diseases. By HARRIET BAILEY, R.N. Second edition completely revised. 294 pp. $2.00. (*The MacMillan Company, New York, 1929.*)

There is so much confusion of thought in the present flood of literature on Psychiatry, that the nursing profession welcomes this revised edition of "Nursing Mental Diseases."

Miss Bailey has covered this particular field of nursing with thoroughness and has dealt with the subject from a point of view that is very helpful for the nurse. She had fully acquainted herself with the latest methods and theories and has handled this complex study with the utmost simplicity and clearness. We are grateful to the author for presenting material which is within the realm of the nurses' needs, without delving into the mysteries and debatable concepts of her subject. We regret, however, that we do not find specific instructions for the handling of actual types of behavior disturbances, but perhaps she feels that this management is too spontaneous a reaction to be dealt with in a textbook.

Miss Bailey has succeeded in producing a book that is a combination of comprehensiveness and practicability. It will undoubtedly prove of great usefulness to students interested in the fundamentals of Psychiatric Nursing and should be found in the libraries of all Training Schools for Nurses.

B. A. M.

The Newer Knowledge of Nutrition. By E. V. McCollum, Ph.D., Sc.D. and Nina Simmonds, Sc.D. (Hygiene). Illustrated. Fourth edition, rewritten. 594 pp. $5.00. (*The MacMillan Company, New York, 1929.*)

This is the fourth edition of Dr. McCollum's 'The Newer Knowledge of Nutrition,' and is somewhat more compact in form than the previous ones. The chapter headings on the various subjects of nutrition are essentially unchanged, but the subject matter has been brought up to date. As in former editions, the portions dealing with the vitamins and dietary deficiency diseases are particularly well done. A large and excellent bibliography has also been added, but unfortunately its usefulness is somewhat impaired by the fact that references to the text are not provided. From the reviewer's point of view, also, it would add materially to its usefulness were the titles of articles also supplied. This edition will undoubtedly continue to uphold the high reputation of the book in the field which it covers.

G. A. H.

Roentgenology. By G. W. C. Kaye, O.B.E., M.A., D.Sc., F. Inst. P. Illustrated. 157 pp. 2.00. (*Paul B. Hoeber, Inc., New York, 1928.*)

This book is an elaboration of the Caldwell Lecture which the author delivered before the American Roentgen-Ray Society.

The early history of roentgenology is treated in a very interesting manner, and the events which led up to the discovery of x-rays by Roentgen are described in chronological order, from the time that Gilbert (1540–1603) first used the word "electricity" in his work "De Magnete," until Roentgen made his discovery in 1895. This portion of the book is well illustrated with cuts which depict the various types of apparatus used by the experimenters as they gradually unfolded the knowledge regarding electricity.

The theories which have been advanced regarding the nature of radiation are concisely but completely explained, and the work relating to reflection, refraction, and difraction of x-rays is carefully evaluated. The experiments regarding the physical properties of the roentgen ray have tremendously increased our knowledge of the ultimate structure of solid matter, but they have not produced a theory which will embrace all their physical characteristics and activities. This is very clearly set forth by the author when he relates the opposing claims of the electromagnetic wave and of the quantum theories.

The portion of the book that deals with roentgen-ray protection is especially important to anyone who operates an x-ray machine, because the results achieved by various investigators regarding the relative value of the different materials used for x-ray protection are very accurately tabulated. The recommendations of the Second International Congress of Radiologists in Stockholm in 1928 for the protection of x-ray and radium workers are given in full. Any one who contemplates the building or operation of an x-ray laboratory would do well to familiarize himself with them.

A large fund of knowledge is contained in this small volume.

J. W. P.

Gynecologic Technique. By THOMAS H. CHERRY, M.D., F.A.C.S. 678 pp. $8.00. (*F. A. Davis Company, Philadelphia, 1929*).

The author has presented adequately the technique of most procedures utilized in both surgical and medical gynecology. The major portion of the work dealing with operative procedures offers nothing new, but briefly and systematically describes the various operations preferred by the author. These are all well recognized and sound procedures, but as there is only one technique presented for each indication, there is considerable room for difference of opinion on the part of well trained gynecologists. This part of the work might be used for teaching purposes but really fills no great need. An adequate knowledge of the operative procedures in any branch of major surgery can only be acquired at the operating table, and men who devote sufficient time in their gynecological training to the acquiring of such knowledge are of necessity familiar with the larger works on gynecology where all the operative procedures herein described and many others are fully treated.

The later sections of the work dealing with medical gynecology and particularly the chapters dealing with the newer procedures such as radium therapy and diathermy are well worth-while. The recommendation for the adequate treatment of chronic endocervicitis as a prophylactic measure in the prevention of carcinoma of the cervix should be seriously considered not only by gynecologists but by every practitioner of medicine. The illustrations demonstrate clearly the desired points, but to one familiar with the Brödel school they leave much to be desired from an artistic point of view.

H. S. E.

Thyroxine. By EDWARD C. KENDALL. pp. 265. $5.50. (*Chemical Catalog Co., New York. 1929.*)

This monograph of the American Chemical Society Series provides a comprehensive review of the literature and opinions relating to Thyroxine and thyroid products in general. After six preliminary chapters on the isolation and chemistry of the substance, in which Harrington's methods of synthesis are fully described and credited, the various phases of its physiologic activity are fully discussed under such headings as Influence on Nitrogen, Phosphorus and Calcium Metabolism, on Water Distribution, Basal Metabolic Rate, Carbohydrate Metabolism and Body Growth. For the laboratory worker additional chapters on the Standardization of Thyroid Materials, Influence on the Metamorphosis of Amphibian Larvae and the part played in Chemical Reactions and Biological Oxidations are of interest. The section on Clinical Aspects of Thyroid Disease is elementary and obviously not at first hand. Plummer's views are constantly drawn upon and one finds Exophthalmic Goitre and Toxic Adenoma strictly differentiated while the inexcusable statement is made that "the two diseases are distinguished by the use of Lugol's solution," the basal metabolic rate and the severity of symptoms falling under its influence in the former but not in the latter. In view of the admittedly

doubtful character of much of the evidence, the chapter on the Influence of the Thyroid on the Nerves might well be briefer.

From the experimental viewpoint it is refreshing to hear a note of warning sounded against too ready acceptance of results gained from "acute experiments" with thyroid products. The monumental studies of von Cyon, Oswald, Furth and others have been largely discredited for this reason and yet each year sees the publication of observations based on the immediate effects of complex thyroid material which might well have been replaced by any good meat soup.

Throughout the monograph an attempt is made to reflect the growing conception that Thyroxine acts as a catalyst and that it plays an important part in the control of certain of the oxidation-reduction reactions within the animal organism. The volume is clearly written and no attempt is made to complete the picture by filling in the gaps, which indeed are freely and frankly indicated; a fact which adds much to the accuracy and the stimulating quality of the material. This monograph will prove valuable to anyone interested in the Thyroid and its problems.

D. McE.

The Immunology of Parasitic Infections. By WILLIAM H. TALIAFERRO, Ph.D. Pp. 414, with 28 illustrations. $6.00. (*The Century Biological Series, The Century Company, New York, 1929.*)

This book is the first published to be devoted entirely to the immunology and serology of the animal parasitic infections. Immunologists and parasitologists generally are unaware of the large amount of immunological work that has been done on infections with animal parasites. This has been due to the fact that the information has been widely scattered and often inaccessible. On account of the lack of such information, physicians, public health laboratory workers, and others interested in the diagnosis of parasitic infections have had to rely almost entirely on clinical findings or routine microscopical examinations. The present work brings together in well organized form the results of over 1300 immunological investigations of the various parasitic diseases and gives precise details of methods for carrying out almost every known serological procedure, such as complement fixation, agglutination, precipitin, cutaneous, and miscellaneous tests applicable to each specific disease. In one chapter is given a summary of the author's own contributions on lytic and reproduction-inhibiting antibodies in trypanosomiasis and malaria. The possibilities of protective and curative immune sera in certain parasitic infections are considered. A chapter on the use of serological and immunological reactions in the classification of animal parasites should be of particular interest to zoologists. The bibliography which, with a few exceptions, is very comprehensive, will be a great aid to research workers and others interested in the subject.

G. H. B.

An Introduction to the Study of Human Anatomy. By R. J. TERRY, A. B., M.D. $3.50. (*The Macmillan Company, New York. 1929.*)

This book introducing human anatomy appears to be a lineal descendant of the Cunningham and Barker types of manual, but with the dual purpose of furnishing not only a set of directions for dissection but also a point of departure for student inquiry. On first impression, at least, the bold array of Latin terms and the solid pages of text, unrelieved by benefits of illustration, would scarcely arouse much interest in anatomy. Nor does one gather from a careful reading of the book that anatomy has any significant relation to the general body of science, pure or applied, except in so far as occasional reference is made to certain pathological conditions.

The question of variation is duly and repeatedly stressed, although its possible meaning is not suggested. However, the mere fact that the student is made aware of variation, and is thereby led to search for things not conforming to the idealized or special case set forth in a textbook does, indeed, mark a step forward in anatomical teaching.

Another interesting feature of the book is the liberal citation of literature interspersed with the text. This and Professor Terry's own questions should do much to further a real spirit of curiosity about gross anatomy, at least among the less vocationally-minded students.

While the book shares with many others the dubious virtues of a dissection guide, its essential value and virility derive from the fact that it corrects the complacent view of anatomy as a completed science.

C. F. DE G.

Aquatic Mammals. Their Adaptations to Life in the Water. By A. BRAZIER HOWELL. Fifty-four illustrations. (*Charles A. Thomas, Springfield, Ill., and Baltimore, 1930.*)

This work is an interesting and exceedingly well-executed investigation of the mechanics of swimming and of the anatomical adaptations and specializations correlated with the various modes of progression seen in different groups of aquatic vertebrates, particularly mammals. The problem is a difficult one, requiring a broad biological perspective, as well as detailed knowledge of comparative antomy, physiology and the life-habits of highly diversified groups of animals. The writer presents and analyses the problem in a thoroughly scientific way which, however, is not so overburdened with facts and uncorrelated data as to become tedious.

The reader is introduced to the subject by a general discussion of the nature and evolution of aquatic life in mammals. The author says: "Almost all mammals can swim after a fashion, and even some of those which one would naturally expect to be least capable of doing so, such as the sloths, can cross broad rivers. To merit the term aquatic, however, a vertebrate must be sufficiently at home in the water so that when near this element it will instinctively seek it for conceal-

ment or escape. It must not only be able to swim with adequate speed but must be able to dive with facility and remain submerged. In almost all cases there is necessary the further corollary that it habitually seeks its food in the water."

All aquatic mammals have, of course, evolved from terrestrial ones and the degree of aquatic specialization is corollary to the amount of connection retained with the land. Mammals undoubtedly took to the water in the first instance in search of prey or as a means of escape from enemies which pursued them. "If in the water a mammal encountered an abundance of enemies in the shape of large fish or hungry reptiles, it might either be exterminated, forced back to face terrestrial enemies as being the lesser of two evils, or obliged to content itself with a borderline existence, foraging in shallow water and protective vegetation. This latter has constituted the fate of most small semi-aquatic insectivores and rodents. Some of them may eventually encounter an environment sufficiently favorable so that they can relinquish such a game of hide and seek and boldly take to the open water." These latter, however, will not become exclusively aquatic as long as the young have to pass their early life upon land. The whales and sirenians have severed this slightest connection with the dry land by contriving to accomplish a completely aquatic birth for their young. Following the introductory exposition of the entire problem, the mechanics of swimming and the morphological adaptations of the body to the aquatic environment are taken up in successive chapters.

The mechanics of swimming are considered from the standpoint of aquatic propulsion (1) by rhythmic undulatory or oscillating movements of the body proper, and (2) by rhythmic movements of the appendages. The former means of propulsion by the body and the base of the tail differs in reference to whether the body is fusiform or anguilliform. The mode of swimming called the fusiform type is seen in whales and sea-cows amongst mammals and can be compared mechanically with the various ways of propelling a boat by sculling. The anguilliform or eel-like progression is encountered only in lower vertebrates—fish and reptiles—with the exception amongst mammals of certain fossil whales (Zeuglodonts).

Propulsion by means of appendageous movements of both fore and hind limbs is characteristic of some species of turtles and many aquatic mammals, comprising the polar bears, walruses, hippopotamuses and capybaras. Propulsion by means of pectoral appendages is observed amongst mammals in the monotremes (Ornithorhynchus) and in the fur seals and sea-lions, while propulsion by pelvic appendages characterizes numerous mammals, namely, certain marsupials and insectivores, the sea-otters, hair seals and many rodents. Amongst the groups that propel themselves by their limbs the most specialized instance is encountered in the sea-lions and fur seals in which the principle is much the same as that of a row-boat.

"Thorough modification for an aquatic life by a mammal involves not only more numerous but more profound anatomical and physiological alterations than for any sort of existence." These adaptations are discussed in a series of excellent chapters upon the external features; the curiously modified visual, acoustic and olfactory apparatuses; the bizarre mouth and nose; and the widely diversified

morphology of the skeleton and musculature of limbs, trunk and tail in the numerous types of aquatic mammals. In these chapters the author reviews critically the more important hypotheses concerning the morphological changes in aquatic mammals brought about through use, and presents a careful analysis of the mode of evolution of the diversified structural adaptations necessitated by an aquatic environment.

G. B. W.

The Neuroses. By ISRAEL S. WECHSLER. 330 pp. $4.00. (*W. B. Saunders Company, Philadelphia, 1929.*)

The author presents the large field of neuroses as an entity, but stresses that there is no definite border to psychoses and that a careful physical examination is essential. His classification, which is entirely based on Freud's teaching, may, unfortunately, efface this valuable principle and lead to a nosological instead of an individual treatment with due attention to all the factors involved. Much space is devoted to a discussion of Freud's psychoanalytic theory and approach. An excellent historical survey gives an idea of the development of psychiatric thought and psychotherapy, but omits, unfortunately, modern American Psychiatry. Instructions for taking histories and intelligence tests, together with a short outline for examination, are most valuable for the practitioner.

O. D.

Pathogenic Microörganisms. By WILLIAM HALLOCK PARK, ANNA WESSELS WILLIAMS and CHARLES KRUMWIEDE. 816 pp. $6.50. (*Lea and Febiger, Philadelphia, 1929.*)

The ninth edition of this standard manual and textbook is enlarged and revised to cover practically the whole field of pathogenic microörganisms. Numerous portions of the book have been completely rewritten and amplified. This is especially true of the sections relating to active immunization against diphtheria and scarlet fever in which the results of an extensive practical experience are presented.

The newer knowledge relative to measles, yellow fever, undulant fever, tularemia and the various types of pneumococci is reviewed and the chapter on complement fixation has been given particular attention. The details of the Kahn, Kline and Meinke precipitation tests have been added.

From the standpoint of the student or clinical pathologist this is without doubt the most accurate and comprehensive book covering the field of the microörganisms pathogenic for man. What commends it most is the fact that the methods and procedures given are based on years of experience in the diagnostic laboratory.

There are, of course, some errors, as might be anticipated in a book of this length and scope. For the most part, however, they are errors of omission. The omission of sodium tellurite agar for the isolation of diphtheria, failure to mention the cataphoresis test in determining virulence of diphtheria or pneumococci

and absence of details regarding the possible differentiation of the beta hemolytic streptococci of human and bovine origin are examples.

S. R. D.

Mammalian Physiology. A Course of Practical Exercises. By E. G. T. LIDDELL and SIR CHARLES SHERRINGTON. 174 pp. 50 text illustrations and 9 colored plates. $5.50. (*Oxford University Press*, 1929.)

The present book is a new edition of Sherrington's well known manual of practical exercises in mammalian physiology, which has been revised with the addition of new matter and one new exercise. The form and general arrangement of the older manual are retained.

Sherrington's unique manual has enjoyed undisputed supremacy as a manual for students working on mammalian preparations. Its thorough yet concise and well organized directions, the helpful illustrations and the pungent annotations could have been written only by one with the experience in this field of work possessed by Sherrington. In this respect it has a distinctive flavor which is refreshing when compared to the usual dull, pedagogic manuals of most authors.

The type of experiment given in the present manual is, however, being gradually and justifiably displaced, in the Medical School curriculum, by experiments performed on man. Physiological laboratory exercises for medical students have passed, from the stage in which the frog was the chief animal of study, to the use of anesthetized and operated mammals, and is finally passing to the use of normal man. However, much of our present knowledge is based on operative experiments and the manual of Liddell and Sherrington will be welcomed by those who have occasion to carry out any of the usual physiological operations on animals.

Owing to the legal restrictions of England regarding animal experimentation, the exercises are all based on the use of a decapitated carcase, and are, therefore, necessarily limited in their application. The American worker, not thus restricted in his teaching, can add many valuable exercises dealing with functions which can be maintained unaltered after the use of one or another of the many available anesthetics.

A. G.

Tuberculosis: Its Prevention and Home Treatment. A Guide for the Use of Patients. By H. HYSLOP THOMSON. 99 pp. 3rd ed. $.75. (*Oxford Medical Publications, 1928.*)

This book is obviously written from the view-point of the Public Health Official and not, as one is accustomed to find in similar works, from that of a personal physician offering helpful details for the comfort and well-being of the afflicted. Accordingly, prevention receives the proper emphasis, occupying the first four chapters, in which the nature of the disease, the preventability, curability, non-infectiousness, causes both predisposing and active, methods of avoiding the disease, and precautions against infection are briefly considered. The next two

chapters discuss the necessity of and requirements for home treatment, followed by a discussion of temperature and body-weight, with detailed instructions as to how they are to be observed, as well as dogmatic statements concerning what should be done under the special conditions outlined. Personal measures regarding rest, exercise, occupation, marriage, etc., are touched upon, and the importance of a routine is emphasized. A short chapter discussing diet forms the remainder of the book, except for a concluding chapter of good advice, telling when to seek medical counsel and giving a rather long, but well-chosen, list of symptoms which should send one to his physician. As a whole, one is impressed with the idea that this little volume will serve well as educational literature for the general public on the prevention of tuberculosis as well as a brief guide past a few of the pitfalls, in the treatment of this disease.

C. S. T.

Diseases of the Chest and the Principles of Physical Diagnosis. By GEORGE W. NORRIS, M.D., and HENRY R. M. LANDIS, M.D. 4th ed. revised. 954 pp. $10.00. (*W. B. Saunders Company, Philadelphia, 1929.*)

This is the fourth time the reviewer has had the opportunity to express his appreciation to the authors for a most serviceable book for the study and teaching of Physical Diagnosis. In each edition the subject matter has been well presented and the appearance of the fourth edition bespeaks the satisfaction of the medical profession. For each two pages of written matter, there is a page illustration, which, in general, represents a picture of the anatomical or pathological anatomical condition discussed in the text. This definite association of pathological changes and physical diagnosis is the distinguishing feature of the book; and must appeal to all clinicians. In 1761 Auenbrugger initiated physical diagnosis, when he insisted that the various percussion phenomena were to be explained by reference to corresponding physical states. Laennec, in 1819, continued this idea in his application of physics to the understanding of various auscultatory findings in health and disease. Obviously, then, the use of this book, where pictures of excellent anatomical specimens (for the most part the work of Fetterhoff) illustrate the text, is in accord with the teachings of the fathers of physical diagnosis. The reviewer sincerely recommends this book to students and practitioners of medicine.

E. W. B.

A History of the Medical Department of the United States Army. By COLONEL P. M. ASHBURN, M.C., U. S. Army. Pp. 432. $5.00. (*Houghton, Mifflin Company, Boston.*)

In this readable volume of some four hundred pages the author has traced the growth and development of the Medical Department of our army from its beginnings in the Revolution, through our various wars and the intervening periods of peace, down to the present time. The subject is logically treated by the periods

into which it naturally falls. The contemporary state of medicine, on the one hand, and of military science and organization, on the other, are summarized, so that we have the evolution of the Medical Department presented in its proper setting.

No complete history of the Medical Department has heretofore appeared and much of the matter here presented now becomes accessible to the general reader for the first time. Much of it, therefore, is of more than ordinary interest. On looking over the book one realizes at once that a great deal of work was necessary to assemble this material and any one who has ever had occasion to search official records will admire the industry of the author. To read it is to appreciate its literary merit, for he tells an interesting and an absorbing story in a frank and pleasing way. It is free from exaggeration, and is accurate and well documented, but is not unduly drawn out or hard to read.

It is a story of hope and disappointment, of achievement and defeat, of greatness and pettiness, but always of growth and development, of progress, through the years, from small to greater things. On the whole, it is a very creditable record, and it is a record that is but little known to the public at large or even to the medical profession. Certain outstanding achievements of the Medical Department, it is true, are well and generally known because of their dramatic nature and far-reaching results. The stories of Beaumont, of Reed and of Gorgas have been told elsewhere and in detail. It seems to us that the chief contribution of this author is that he makes accessible the record of other accomplishments, some of them the work of outstanding individuals, individuals who for one reason or another have been passed by fame; others that have had a slow fruition over a period of years, as a result of the activities of a number of inconspicuous men. So it is that those fortunate occasions when a Beaumont or a Reed pushed back the frontiers of knowledge are well known; less well known are the trials and achievements of a Letterman or a Hammond; and lost in obscurity are the names of those men who, through the years, have maintained a high standard of medical service in our army, kept abreast of the times, often in the face of almost insuperable difficulties, and whose combined labors have had such important, if less dramatic, results in war and in peace. The progressive lowering of the death rate and of the disease incidence rate of our army is no small thing. Not only has yellow fever disappeared and typhoid been virtually abolished but the incidence of rheumatic fever has been decreased by ninety per cent in the past quarter century and even venereal disease has been reduced by more than sixty per cent.

In these achievements the author himself has had his part. His active service in the Medical Department covers thirty-two years and two wars. Of this period he writes as an eye-witness and an active participant. His book on military hygiene is one of the reasons why the average line officer of today knows more of military hygiene and sanitation than did the average medical officer of the Civil War and the Spanish War.

To the military reader, both of the line and of the Medical Department, active

and reserve, the book will be invaluable. The general reader will find it an interesting and a fascinating story in the sense that all history is interesting and fascinating if properly presented. Those who are interested in the history of medicine will find here much new material. It is especially commended, however, to those who have been members of the Medical Department in the past or who may become members of it in the future, should the need arise.

E. E. C.

BOOKS RECEIVED

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. with the collaboration of Chas. H. Mayo, M.D. Thirty-ninth series. Vol. IV. 1929. 8°. 308 pages. J. B. Lippincott Company, Philadelphia.

Handbook of Bacteriology for Nurses. By HARRY W. CAREY, A.B., M.D. Third revised and enlarged edition. Illustrated with forty-three engravings and one colored plate. 1930. 8°. 282 pp. F. A. Davis Company, Philadelphia. $2.25.

The Immunology of Parasitic Infections. By WILLIAM H. TALIAFERRO, Ph.D. The Century Biological Series. 1929. 8°. 414 pages. The Century Company, New York. $6.00.

Ueber Röntgenschäden und Schäden durch radioaktive Substanzen. Von PRIV.-DOZ. DR. WILHELM FLASKAMP. Mit einem Geleitwort von Prof. Dr. Med. et Phil. Hermann Wintz. Mit 94 Bildern, 30 Tafeln und 6 Tabellen. Sonderbände zur Strahlentherapie. Band XII. 1930. 4°. 265 Seiten. Urban u. Schwarzenberg, Berlin. RM. 34.

Die Bangsche Krankheit beim Menschen. Von DR. GUSTAV SPENGLER. 1929. 4°. 54 Seiten. Urban u. Schwarzenberg, Berlin. RM. 4.

Otologic Surgery. By SAMUEL K. KOPE, M.D., F.A.C.S. Second revised edition. 1929. 8°. 553 pp. Paul B. Hoeber, Inc., New York.

Research and Medical Progress and Other Addresses. By J. SHELTON HORSLEY, M.D. 1929. 12°. 208 pp. The C. V. Mosby Company, St. Louis. $2.00.

The Neck. A Roentgenological Study of the Soft Tissues. Consideration of the Normal and Pathological. By PERCY D. HAY, JR., M.D. Introduction by Henry K. Pancoast, M.D. Sixty-six roentgen-ray studies. 1930. 8°. 104 pages. Annals of Roentgenology, Vol. IX. Paul B. Hoeber, Inc., New York. $8.00.

Essentials of Medical Electricity. By ELKIN P. CUMBERBATCH, M.A., B.M. (Oxon.), D.M.R.E. (Camb.), M.R.C.P. Sixth edition, revised and enlarged. With eleven plates and 116 illustrations. 1929. 8°. 443 pp. The C. V. Mosby Company, St. Louis. $4.25.

The Mechanism of the Larynx. By V. E. NEGUS, M.S., London, F.R.C.S., England. With an introduction by Sir Arthur Keith, F.R.S. Illustrated. 1929. 8°. 528 pages. The C. V. Mosby Company, St. Louis. $13.50.

A System of Bacteriology in Relation to Medicine. By C. H. BROWNING, W. BULLOCH, J. H. DIBLE, A. FLEMING and others. (Medical Research Council) Vol. 2. 1929. 8°. 420 pp. His Majesty's Stationery Office, London. $5.15.

Hypertension and Nephritis. By ARTHUR M. FISHBERG, M.D. Illustrated with 33 engravings and 1 colored plate. 1930. 8°. 536 pp. Lea and Febiger, Philadelphia. $6.50.

The Pathology of the Eye. By JONAS S. FRIEDENWALD. A.M., M.D., F.A.C.S. Illustrated with 253 figures, mainly microphotographs from the Pathological Collections of the Wilmer Ophthalmological Institute and the Army Medical Museum. 1929. 8°. 347 pp. The MacMillan Company, New York. $4.50.

Urologie Pratique. Par DR. P. BAZY. 1930. 8°. 535 pp. Gauthier-Villars et Cie, Paris.

The Principles of Bacteriology and Immunity. By W. W. C. TOPLEY, M.A., M.D., M.Sc., F.R.C.P. and G. S. WILSON, M.D., M.R.C.P., D.P.H. Volumes I and II. 1929. 8°. 1320 pages. William Wood and Company, New York.

Getting Well and Staying Well. By JOHN POTTS, M.D. Introduction by J. B. McKnight, M.D. Second edition. 1930. 12°. 221 pp. The C. V. Mosby Company, St. Louis. $2.00.

Nursing in Emergencies. By JACOB K. BERMAN, A.B., M.D., F.A.C.S. With one hundred nine illustrations. 1929. 12°. 160 pp. The C.V. Mosby Company, St. Louis. $2.25.

Symptoms of Visceral Disease. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P. Fourth edition. With 87 text illustrations and 10 color plates. 1930. 8°. 426 pages. The C. V. Mosby Company, St. Louis. $7.50.

Practical Psychology and Psychiatry. By C. B. BURR M.D., Sixth edition, revised and enlarged, with illustrations. 1930. 8°. 378 pages. F. A. Davis Company, Philadelphia. $2.75.

Tonsil Surgery. Based On a Study of the Anatomy. By ROBERT H. FOWLER, M.D. 103 Illustrations, including 10 full-page color plates. 1930. 4°. 288 pp. F. A. Davis Company, Philadelphia. $10.00.

A Text-Book on Orthopedic Survery. By WILLIS C. CAMPBELL, M.D., F.A.C.S. Illustrated. 1930. 8°. 705 pp. W. B. Saunders Company, Philadelphia. $8.50.

Treatment in General Practice. By HARRY BECKMAN, M.D. 1930. 8°. 899 pp. W. B. Saunders Company, Philadelphia. $10.00.

The Nursing of Infectious Diseases. By J. J. WOOLLACOTT, M.A., M.D., B.CH. Oxon., D.P.H. Revised and Enlarged by Dorothy C. Hare, C.B.E., M.D., M.R.C.P., D.P.H. 1930. 12°. 195 pp. G. P. Putnam's Sons, New York. $1.50.

A Textbook of Orthopaedic Nursing. By EVELYN C. PEARCE. With a Foreword by Sir Robert Jones, Bart., K.B.E., C.B., F.R.C.S. and an Introductory Chapter by Dame Agnes Hunt, D.B.E., R.R.C. 1930. 12°. 155 pp. G. P. Putnam's Sons, New York. $1.75.

Gynaecology for Nurses and Gynaecological Nursing. By COMYNS BERKELEY, M.A., M.D., Cantab., F.R.C.P. Lond., F.R.C.S. Eng. Revised and enlarged. 1930. 12°. 426 pp. G. P. Putnam's Sons, New York. $2.75.

Surgical Diagnosis. By 42 American Authors. Edited by Evarts Ambrose Graham, A.B., M.D. Containing 1250 illustrations. 1930. 8°. Vol. I, 919 pages; Vol. II, 871 pp. W. B. Saunders Company, Philadelphia. $10.

The Modern Dance of Death. By PEYTON ROUS. The Linacre Lecture, 1929. 12°. 51 pages. Cambridge University Press, Cambridge.

L'Hydrothérapie Médicale. Par. R. DUBOIS DE SAUJON. 1930. 8°. 127 pp. Les actualités physiothérapiques. Hydrothérapie, VI. Gauthier-Villars et Cie, Paris.

The Baby's First Two Years. By RICHARD M. SMITH, A.B., M.D., Sc.D. With illustrations. New and revised edition. 1930. 16°. 159 pp. Houghton Mifflin Company, Boston. $1.75.

Oxford Medical Publications. Publisher: Humphrey Milford, London. The following four volumes:

Mammalian Physiology. A Course of Practical Exercises. By E. G. T. LIDDELL, D.M., Fellow of Trinity College Oxford and SIR CHARLES SHERRINGTON, O.M., M.D., D.Sc. (Cantab.), F.R.S. New edition. 1929. 4°. 162 pp. $5.50..

A Textbook of the Practice of Medicine. By Various Authors. Edited by Frederick W. Price, M.D., F.R.S. (Edin.). Third edition. 1929. 8°. 1871 pp. $11.50.

Surgery of the Lung and Pleura. By H. MORRISTON DAVIES, M.A., M.D., M. Ch. (Cantab.) F.R.C.S. (England). 1930. 8°. 355 pp.

Applied Physiology. By SAMSON WRIGHT, M.D., M.R.C.P. With Introduction by Swale Vincent, M.D., LL.D., D.Sc., F.R.S. (Ed. & Canada). Third edition. 1929. 8°. 552 pages.

Physician and Patient. Personal Care. Edited by L. Eugene Emerson. 1929. 8°. 244 pages. Harvard University Press, Cambridge.

The Challenge of Chronic Diseases. By ERNST P. BOAS, M.D., and NICHOLAS MICHELSON, M.D. 1929. 12°. 197 pages. The Macmillan Company, New York. $2.50.

State Board Questions and Answers. By R. MAX GOEPP, M.D. Sixth edition, thoroughly revised. 1929. 8°. 754 pages. W. B. Saunders Company, Philadelphia. $6.00.

Physical Examination and Diagnostic Anatomy. By CHARLES B. SLADE, M.D. Fourth edition, thoroughly revised. 1929. 12°. 196 pages. W. B. Saunders Company, Philadelphia. $2.00.

American Illustrated Medical Dictionary. With the Pronunciation, Derivation, and Definition. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S. Fifteenth edition, revised and enlarged. 1929. 8°. 1427 pages. W. B. Saunders Company, Philadelphia. $7.50.

Gynecologic Technic. By THOMAS H. CHERRY, M.D., F.A.C.S. With 558 half-tone and line engravings, from photographs and pen and ink drawings by the author. 1929. 8°. 678 pages. F. A. Davis Company, Philadelphia. $8.00.

Varicose Veins. With Special Reference to the Injection Treatment. By H. O. MCPHEETERS, M.D., F.A.C.S. Illustrated with half-tone and line engravings. 1929. 8°. 208 pages. F. A. Davis Company, Philadelphia. $3.50.

The Anatomy and Physiology of Capillaries. By AUGUST KROGH, Ph.D., LL.D. Revised and enlarged edition. 1929. 8°. 423 pages. Yale University Press, New Haven. $4.00.

The History of Nursing. By JAMES J. WALSH, M.D., Ph.D. 1929. 12°. 293 pages. P. J. Kennedy & Sons, New York. $2.00.

Recent Advances in Surgery. By W. HENEAGE OGILVIE, M.A., M.D., M.Ch., Oxon., F.R.C.S. Eng. Second edition. With 115 illustrations. 1929. 12°. 495 pages. P. Blakiston's Son & Company, Philadelphia. $3.50.

Sterilization for Human Betterment. By E. S. GOSENY, B.S., LL.B., and PAUL POPENOE, D.Sc. 1929. 12°. 202 pages. The Macmillan Company, New York. $2.00.

Minor Surgery. By FREDERICK B. CHRISTOPHER, M.D. With a foreword by Allen B. Kanavel, M.D., 1929. 8°. 694 pages. W. B. Saunders Company, Philadelphia. $8.00.

Handbuch der Biologischen Arbeitsmethoden. Herausgegeben von Geh. Med.—Rat Prof. Emil Abderhalden. Abt. IV. Angewandte Chemische und Physikalische Methoden, Teil 6, 2. Hälfte, Heft 4. 1928. 8°. 120 Seiten. Urban u. Schwarzenberg, Berlin.

Travaux de L'Institut de Sérologie. Par PROF. DR. J. CANTACUZÈNE. T. I. 1928. 8°. 503 pages. Masson et Cie, Paris.

Coxite Gonococcique. Par DR. MARTHE LAMY. 1929. 8°. 250 pages. Gauther-Villars et Cie, Paris.

Pathogenic Microörganisms. A Practical Manual for Students, Physicians and Health Officers. By WILLIAM HALLOCK PARK, M.D., ANNA WESSELS WILLIAMS, M.D., and CHARLES KRUMWIEDE, M.D. Ninth edition, enlarged and thoroughly revised with 216 engravings and 9 full-page plates. 1929. 8°. 819 pages. Lea & Febiger, Philadelphia. $6.50.

The Chemical Aspects of Immunity. By H. GIDEON WELLS, Ph.D., M.D. Second (revised and enlarged) edition. American Chemical Society Monograph Series. 1929. 8°. 286 pages. The Chemical Catalog Company, New York. $6.00.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic and

Physiological Chemistry for Nurses and Students of Home Economics and and Applied Chemistry, With Laboratory Experiments. By JOSEPH H. ROE, Ph.D. Second edition. 12°. 427 pages. The C. V. Mosby Company, St. Louis. $2.50.

Outline of Preventive Medicine. For Medical Practitioners and Students. Prepared Under the Auspices of the Committee on Public Health Relations, New York Academy of Medicine. Editorial Committee, Frederic E. Sondern, Chas. Gordon Heyd, and E. H. L. Corwin. 1929. 12°. 398 pages. Paul B. Hoeber, Inc., New York. $5.00.

Recent Advances in Cardiology. By C. F. TERENCE EAST, M.A., M.D. (Oxon.) F.R.C.P. (Lond.) and C. W. CURTIS BAIN, M.C., M.B. (Oxon.), M.R.C.P. (Lond.). With 12 plates and 57 text-figures. 1929. 12°. 324 pages. P. Blakiston's Son and Company, Philadelphia. $3.50.

Materia Medica and Therapeutics. Including Pharmacy and Pharmacology. By REYNOLD WEBB WILCOX, M.A., M.D., LL.D., D.C.L. Twelfth edition revised in accordance with the United States Pharmacopoeia X and the National Forumlary V. With an index of symptoms and diseases. 1929. 8°. 690 pages. P. Blakiston's Son and Company, Philadelphia. $5.00.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. with the collaboration of Chas. H. Mayo, M.D. Thirty-ninth series, volume III. 1929. 8°. 308 pages. J. B. Lippincott Company, Philadelphia.

A System of Bacteriology in Relation to Medicine. By W. BULLOCK, P. FILDES, A. T. GLEENY, H. HENRY, R. T. HEWLETT and others. Medical Research Council, volume III. 1929. 8°. 413 pages. His Majesty's Stationery Office, London. 51/.

Tularemia. History, Pathology, Diagnosis and Treatment. By WALTER M. SIMPSON, M.S., M.D., F.A.C.P. Foreword by Edward Francis. With 53 text illustrations and 3 colored plates. 1929. 8°. 162 pages. Paul B. Hoeber, Inc., New York. $5.00.

Intern's Handbook. A Guide to Rational Drug Therapy, Clinical Procedures and Diets. By Members of the Faculty of the College of Medicine, Syracuse University. Under the Direction of M. S. Dooley, A.B., M.D. 1929. 16°. 254 pages. $3.00.

An Introduction to the Study of Human Anatomy. By ROBERT JAMES TERRY, A.B., M.D. 1929. 8°. 346 pages. The Macmillan Company, New York. $3.50.

Recent Advances in Tropical Medicine. By SIR LEONARD ROGERS, C.I.E., M.D., B.S. (Lond.), F.R.C.S., F.R.S. Second edition. With 16 illustrations 1929. 12°. 439 pages. P. Blakiston's Son and Company, Philadelphia. $3.50.

Diseases of Women. Symptoms and Treatment. By FRANKLIN I. SHROYER, M.D. 1929. 12°. 103 pages. Richard G. Badger, Publisher, Boston.

Three Minute Medicine. A Series of Brief Essays on Popular Medicine. By LOUIS R. EFFLER, A.M., M.D. 1929. 12°. 453 pages. Richard G. Badger, Publisher, Boston.

The Female Sex Hormone. By ROBERT T. FRANK, A.M., M.D., F.A.C.S. Part I. Biology, Pharmacology and Chemistry. Part II. Clinical Investigation Based on the Female Sex Hormone Blood Test. With 86 illustrations and 36 graphs. 1929. 8°. 321 pages. Charles C. Thomas, Springfield. $5.50.

Clinical Medicine for Nurses. By PAUL G. RINGER, A.B., M.D. Illustrated. Third revised edition. 1929. 12°. 330 pages. F. A. Davis Company, Philadelphia. $3.00.

The Nutrition of Healthy and Sick Infants and Children. For Physicians and Students. By E. NOBEL, C. PIRQUET, and R. WAGNER. Second revised edition with 78 illustration (including charts) and 6 tables. Authorized Translation by Benjamin M. Gasul, B. S., M.D. 1929. 8°. 243 pages. F. A. Davis Company.

Surgical Diseases of the Thyroid Gland. By E. M. EBERTS, M.D. With the Assistance of R. R. FITZGERALD, M.D., and PHILIP G. SILVER, M.D. Illustrated with 48 engravings. 1929. 8°. 238 pages. Lea and Febiger, Philadelphia. $3.50.

Practical Local Anesthesia. And Its Surgical Technic. By ROBERT EMMETT FARR, M.D., F.A.C.S. Second edition, thoroughly revised. Illustrated with 268 engravings and 16 plates. 1929. 8°. 611 pages. Lea and Febiger, Philadelphia. $9.00.

Diseases of the Chest and the Principles of Physical Diagnosis. By GEORGE WILLIAM NORRIS, A.B., M.D., and HENRY R. M. LANDIS, A.B., M.D., Sc.D. With a Chapter on the Transmission of Sounds Through the Chest by Charles M. Montgomery, M.D. and a Chapter on the Electrocardiograph in Heart Disease by Edward B. Krumbhaar, Ph.D., M.D. Fourth edition, revised. 1929. 8°. 954 pages. W. B. Saunders Company, Philadelphia. $10.00.

Text-Book of Embryology. By FREDERICK RANDOLPH BAILEY, A.M., M.D., and ADAM MARION MILLER, A.M. Fifth revised edition. With 526 illustrations. 1929. 8°. 687 pages. William Wood and Company, New York. $7.00.

Modern Methods of Treatment. By LOGAN CLENDENING, M.D. With Chapters on Special Subjects. By H. C. Anderson, M.D.; J. B. Cowherd, M.D.; H. P. Kuhn, M.D.; Carl O. Ricketer, M.G.; F. C. Neff, M.D.; E. H. Skinner, M.D.; and E. R. DeWeese, M.D. Third edition. 1929. 8°. 815 pages. C. V. Mosby Company, St. Louis. $10.00.

The Blood Picture and its Clinical Significance. (Including Tropical Diseases.) A Guidebook on the Microscopy of Blood. By PROF. DR. VICTOR SCHILLING. Translated and edited. By R. B. H. Gradwohl, M.D. Seventh and eighth revised edition with 44 illustrations and 4 color plates. 1929. 8°. 408 pages. C. V. Mosby Company, St. Louis, $10.00.

Oxford Medical Publications. Publisher: Humphrey Milford, London. The following ten volumes.

The Principles of Electrotherapy and their Practical Application. By W. J. TURRELL, M.A., D.M., B.Ch. (Oxon.), D.M.R. & E. (Cantab). Second edition. 1929. 8°. 413 pages.

Artificial Sunlight and Its Therapeutic Uses. By FRANCIS HOWARD HUMPHRIES, M.D. (Brux.), F.R.C.P. (Edin.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), L.M. (Rot., Dublin), D.M.R.&E. (Cantab.). Fifth edition. 1929. 8° 340 pages.

Gastro-Intestinal Diseases. Lectures delivered at the James Mackenzie Institute for Clinical Research, St. Andrews Winter Session, 1927. Edited by Professor David Waterston, M.A., M.D., F.R.C.S. (Edin.). 1928. 8°. 278 pages.

The Treatment of Fractures and Dislocations in General Practice. By C. MAX PAGES, D.S.O., M.S. (Lond.), F.R.C.S. and W. ROWLEY BRISTOW, M.B., B.S. (Lond.), F.R.C.S. Third Edition. 1929. 8°. 284 pages.

Ker's Infectious Diseases. A Practical Textbook. Revised by Claude Rundle, O.B.E., M.D. (Lond.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), D.P.H. Third Edition. 1929. 8°. 614 pages.

Endocrine Disorders. By PROFESSOR HANS CURSCHMANN. With an introduction by Franz Prange, Doctor of Medicine and Philosophy: Assist. at the Med. Cl. Univ. of Rostock i.m. 1929. 8°. 188 pages.

Some Principles of Minor Surgery. By ZACHARY COPE, M.S., M.D. (Lond.), F.R.C.S. (Eng.), 1929. 8°. 159 pages.

An Introduction to Pharmacology and Therapeutics. By J. A. GUNN, M.D., D.Sc. (Edin.); M.A. (Oxon.). 1929. 16°. 220 pages.

The Principles of Clinical Pathology in Practice. A Guide to the Interpretation of Laboratory Investigations for the Use of Those Engaged in the Practice of Medicine. By GEOFFREY BOURNE, M.D. (Lond.) M.R.C.P., and KENNETH STONE, M.D. (Oxon.), M.R.C.P. 1929. 8°. 392 pages.

Gastric and Duodemal Ulcer. By ARTHUR F. HURST, M.A., M.D. (Oxon.) F.R.C.P. and MATTHEW J. STEWART, M.D. (Glasg.), F.R.C.P. With the Co-operation in the Radiological Sections of P. J. Briggs, M.A. (Cantab.), M.R.C.S., L.R.C.P. 1929. 8°. 544 pages. $20.00.